DRAFT RESPONSES TO COMMENTS SUBMITTED BY THE WESTERN STATES PETROLEUM ASSOCIATION (WSPA)

Comment 1: CANCER UNIT RISK

The study of railroad workers by Garshick et al. (1987, 1988) that OEHHA used to calculate a lung cancer unit risk is not appropriate and the lung cancer unit risk based on this study is not valid.

HEI (1999) and others (Crump, 1999) conclude this study is not appropriate for a quantitative risk assessment (QRA) for several reasons.

- The exposure data is inadequate because it is based on current levels and not on exposures that occurred during the study period and confounding exposures were not adequately dealt with.

- The evidence for a positive association rests entirely on differences in risks among job categories. However, within all job categories there was a negative association with years worked. A negative exposure-response trend was also observed based on quantitative measures of cumulative exposure (Crump, 1999).

- Latency is too short and there was incomplete follow-up of the cohort. The follow-up in the last 4 years (and perhaps years before that) was incomplete. If those four years are not included in the analysis, then the maximum latency is only 17 years. This latency is too short to adequately estimate risk of lung cancer.

Response: The validity and applicability of the diesel exhaust cancer unit risk factor (URF) have been thoroughly documented in the diesel exhaust Toxic Air Contaminant (TAC) document and will not be discussed further in this document. Responses to specific comments provided by Crump and by HEI were given in Appendix C, Volume 3-1 of that document. The TAC document includes a section on the uncertainties inherent in extrapolating from the quantitative cancer risks associated with occupational diesel exhaust exposure to the quantitative cancer risks

associated with ambient exposure. The prioritization summary for benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons (PAHs) describes data indicating that infants and children are more sensitive than adults to the carcinogenic effects of PAHs. Since diesel exhaust contains a variety of PAHs (among other known and suspected carcinogens), the diesel exhaust URF, which is based on adult occupational exposures, may underestimate the cancer risk to infants and children.

Comment 2: DIESEL EXHAUST AS A LUNG CARCINOGEN. The case for DEP as a lung carcinogen is incompletely documented and not convincingly demonstrated by OEHHA.

The question of causality is a difficult and controversial one where some have a contrary point of view with respect to both causality and control of smoking (Stober and Abel, 1996; Muscat and Wynder, 1995). It would be helpful to acknowledge that there is not a monolithic view that diesel or ambient PM (particulate matter) are carcinogenic. And not all agree that there has been adequate adjustment for smoking, which poses a much greater risk than diesel exhaust.

Response: Diesel exhaust was identified as a carcinogen during the process of identification as a TAC, by a process involving extensive scientific analysis, public comment and peer review. This conclusion is supported by the classification of diesel exhaust as a probable human carcinogen (Class 2A) by the International Agency for Research on Cancer. OEHHA has neither the mandate nor the intention to review this conclusion during the present process. OEHHA has not proposed or assumed the identification of general ambient particulate material (PM) as carcinogenic, but only that PM derived from diesel exhaust.

Comment 3: The risk should be quantified by establishing exposure-response relationships. The OEHHA has cited only the Garshick et al. study of railroad workers, which shows a negative association but has other problems to the extent that the validity of trends are questionable at best, as noted above. Both the Steenland et al. (1998) study of truck drivers and the railroad study have not adequately estimated exposures (HEI, 1999). In addition, a valid exposure-response relationship cannot be estimated unless the exposed workers have adequate latency.

But it was not possible to precisely determine latency because diesels were gradually introduced in these industries and date of first exposure for individual workers could not be determined. Around 1959 gasoline and steam engines were replaced by diesel engines, and was assumed to mark the beginning of diesel exposure in these industries (i.e., no diesel exposure prior to 1959 and only diesel exposure after 1959). However, this categorization results in exposure misclassification as some workers had diesel exposure before 1959 and some continued to have non-diesel exposure after 1959. So latency was too short for some and perhaps long enough for others, but it could not be determined which was which. Essentially all the other occupational studies of diesel exposed workers were published before the average of about 20-years latency could be attained. Without adequate latency time, the estimates of risk will be incorrect because cases will be included who have a latency that is too short to be attributed to DEP. And if DEP does increase the risk of lung cancer the risk ratios (RR) may be low because there has not been adequate latency for the disease to be detected. But the direction and magnitude of these biases are unknown in these studies.

There are two additional occupational studies of lung cancer not considered by OEHHA. These are cohort mortality studies of coal miners (Johnston et al., 1997) and potash miners (Saverin et al., 1999) with internal analyses comparing exposed to nonexposed miners. While these studies also have short latencies, the estimates of cumulative exposure are based on precise and documented dates when diesel exposure actually began and so do not have the uncertainty regarding individual-level latency found in the studies of railroad and truck driver cohorts.

Response: As noted in the response to Comment 1, the validity and applicability of the diesel exhaust cancer unit risk factor (URF) have been thoroughly documented in the diesel exhaust Toxic Air Contaminant (TAC) document, and will not be discussed further. That document includes a section on the uncertainties inherent in extrapolating from the quantitative cancer risks associated with occupational diesel exhaust exposure to the quantitative cancer risks associated with ambient exposure. A meta-analysis comparing the many studies in the scientific literature was published (Lipsett and Campleman, 1999, cited in the OEHHA prioritization document); this found overall consistency between the different studies and a relative risk for lung cancer of 1.43 (1.31-1.57). The prioritization summary for benzo[*a*]pyrene and other polycyclic aromatic

hydrocarbons (PAHs) describes data indicating that infants and children are more sensitive than adults to the carcinogenic effects of PAHs. Since diesel exhaust contains a variety of PAHs, the diesel exhaust URF range, which is based on adult occupational exposures, may be different for infants and children than for adults.

Comment 4: By inference OHHEA suggests that air pollution is associated with an increased risk of lung cancer for the general population. OEHHA cited the HEI (1995) review and results from the Six Cities cohort (Dockery et al, 1993), the American Cancer Society cohort (Pope et al., 1995) and the California cohort called AHSMOG (Mills et al., 1991) as evidence that is consistent with the idea that air pollution increases the risk of lung cancer. However, further analysis of the Six Cities and American Cancer Society (ACS) cohorts does not show an association of lung cancer with fine PM (Krewski et al., 2000). For example the Relative Risk (RR) in Six Cities was 1.03 (0.75-1.41) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ using the extended model and alternative indices for occupational exposure. In the ACS study the RR was 1.00 (0.91-1.11) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ using the model with calendar year time axes. The updated AHSMOG study is internally inconsistent with a significantly increased risk of lung cancer mortality among males of 1.65 (1.21-2.27) but not females who had a nonsignificant RR of 1.13 (0.81-1.57) per 10 $\mu g/m^3$ increase in PM_{10} (Abbey et al., 1999). Nyberg et al. (2000) used NO_2 as a surrogate measure for road traffic in Stockholm and found a nonsignificant RR of 1.17 (0.84-1.62) for the top 90% of exposures estimated for the past 30 years. The only statistically significant finding was an association with a 20-year lag, which could be a chance finding given the large number of comparisons. None of these studies have measured DEP and so cannot assess the lung cancer risk associated with DEP. This illogical inference is discussed in the next section.

Response: The comment implies that we cited an HEI report that reviewed the results of studies on PM10 and mortality. In fact, that is not the HEI report we are citing. The report we cite was specifically on the association between occupational exposures to diesel exhaust and lung cancer (HEI, 1995), and not the excellent review by HEI of the data from the six-cities study and the ACS study (HEI, 2000; Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations authored by Lippman et al.). Thus, the comment's criticism that

we used this report as evidence of the carcinogenicity of diesel exhaust or even PM10 is erroneous.

Consideration of the effects of PM was the subject of a thorough review prepared for, and accepted by, the Air Quality Advisory Committee as part of the review of this criteria air pollutant under SB 25. This review is appended as Appendix A in the back of these responses to comments. Note that this report underwent public comment and peer review and was adopted by the Air Resources Board during the prioritization of criteria air pollutants for review of the standards for adequacy to protect infants and children. OEHHA is well aware of, and has described, the uncertainties in determining the extent of carcinogenic risk from ambient air pollution. It may be concluded that while these uncertainties certainly fall short of the level of definitive proof that one might hope for in any individual study, the overall body of evidence certainly fails to remove the concern that there is a possible carcinogenic effect. Thus, the overall weight of evidence is such as to reinforce that concern. Finally, the association of diesel exhaust particulate with lung cancer is clear.

Comment 5: NONCANCER EFFECTS. OEHHA cites a number of ecological or semi-ecological air pollution studies to infer that DEPs are associated with adverse respiratory effects. This inference is based on a class of studies that have built-in uncertainties, particularly with regard to exposure assessment. In addition OEHHA discusses PM studies and infer that these studies provide evidence that the associations with PM are associations for DEP. These "invited inferences" (Vital Stats, 2001) are not discussed (that is why they are "invited inferences"), and are logically false. Comments regarding noncancer effects attributed to DEP are grouped by characteristics that increase the uncertainty in the OEHHA conclusions.

Uncertainties surround the problem of exposure. Exposure to DEP is not known as it is never measured and the DEP content of PM_{10} is variable and unmeasured. In some studies even PM10 is not measured and so extrapolations made from sulfate or ozone increase even more the uncertainties regarding DEP exposure.

There are inconsistent results that increase uncertainty about the hypothesis. For example in some instances there are stronger associations with ozone than with PM_{10}. At times the

associations between PM_{10} and respiratory effects (asthma) are not with the most relevant or important indicators of asthma, and the lack of associations with relevant indicators, which is not mentioned by OEHHA, detracts from the evidence for an effect. Where both adults and children are in the study population the studies reviewed did not show perceptible differences in effects related to exposure, findings which do not support the hypothesis that children are more susceptible to the effects of ambient PM. Where differences in susceptibility are not expected (as in girls compared to boys) the associations with PM are different. Where differences in susceptibility are expected (as in low birth weight infants compared to normal birth weight infants), the associations with PM are not significantly different. These inconsistencies detract from the hypothesis that DEP (via PM_{10}) causes the adverse health effects postulated by OEHHA in this document.

Confounding is always a concern in observational studies. Individual-level risk factors are not always adequately adjusted for and sometime are not included in the statistical models. Lack of adequate control is particularly important when the associations are weak, as they mostly are, and inadequate or no control often leads to incorrect conclusions. For example, socioeconomic status is associated with nearness to traffic, increased indoor exposure to pollutants, and to increased respiratory symptoms. Adjustment for SES is difficult, education may only partially control for SES, and sometimes there is no information on SES. Confounding can be also occurring in nationwide studies because of differences in mortality rates (for example) in different regions of the country. Adjustments must be made for spatial confounders, which has been demonstrated for both adult mortality and infant mortality.

Factual errors in the OEHHA interpretation of a number of studies detract from the weight of evidence for the hypothesis. The addition of studies that were not included (particularly when they are largely negative studies) has a similar effect on the weight of evidence. A recently published study on infant mortality is particularly important in that there are only two studies cited by OEHHA. The added study takes account of more confounding factors and contradicts the other U.S. study cited and is not consistent with the hypothesis that PM10 or DEP increases infant mortality.

Response:

In the case of DEP, adverse noncancer health effects were clearly identified in the diesel exhaust TAC document (and the US EPA RfC derivation which was included as an appendix to that document). This conclusion has already been the subject of extensive discussion and peer review. The discussion of PM_{10} and $PM_{2.5}$ effects is the subject of a very extensive literature going back many years: a recent re-evaluation of the importance of these effects for both adults and children was undertaken as part of the process for evaluating the criteria pollutants under SB25, and that report is provided as Appendix A to this compilation of comments and responses.

Since the purpose of the current review was to identify any potential for differential effects on infants and children, OEHHA concentrated on those studies which contained information on this issue, and did not include in the toxicity summary a number of studies which are uninformative on this point due to lack of juvenile subjects, lack of power, inadequate exposure assessment or other reasons. There are studies cited in our report that demonstrate impacts on infant mortality of PM10. Infant and child mortality has been associated with acute exposures to PM10 pollution in a number of studies in Mexico (Loomis et al., 1999), Dehli (Cropper et al., 1997), and Bangkokm (Ostro et al., 1998). Other studies have linked infant mortality in the U.S. (Woodruff et al., 1997), and the Czech Republic (Bobak and Leon, 1999) to long-term exposures to PM. In addition, data from the 1952 London smog episode clearly show increases in infant mortality (Bates, 1995).

Comment 6:

A. Exposure Assessment

- The epidemiology studies use only group-level (ecological) measures of exposure that are subject to the ecological fallacy (i.e., it may not be true that the associations observed at the group-level pertain to the individual). The direction and magnitude of the biases that are inherent in such studies are unknown at present, and when tested the bias appears to result in overestimates of the RR (Gamble, 1998; Gamble and Nicolich, 2000).

- None of the air pollution studies are studies of diesels per se because DEP is never explicitly measured. OEHHA says diesel exhaust particles (DEPs) "contribute to ambient air particulate pollution," and these particles 10 microns or less in size (PM_{10}) have been "associated with adverse respiratory health effects in children." Therefore the reader is encouraged to make the invited inference that DEP is associated with the adverse health effects. The logic of the unexpressed inference can be seen clearly in the following diagram:

$$\begin{aligned} \text{DEP} &\rightarrow \text{A portion of ambient } PM_{10} \\ \text{A portion of } PM_{10} &\rightarrow \text{A portion of mortality and morbidity} \\ \text{Therefore DEP} &\rightarrow \text{A portion of mortality and morbidity} \end{aligned}$$

The first two elements in this syllogism are logically and possibly factually correct, but the conclusion is not a logical conclusion. Associations based on PM_{10} without any evidence about DEP do not make the association between DEP and a portion of mortality and morbidity. The logic is incorrect because there is a lack of evidence that the portion of PM_{10} which comes from DEP is the same portion that is possibly associated with some mortality and morbidity. What is unknown is what OEHHA is attempting to prove in this document. Assuming this syllogism is correct is not proof and is not based on scientific reasoning.

- None of the pollutants measured are appropriate surrogates for DEP (Winer and Busby, 1995). Ambient PM concentrations are not an appropriate estimate of exposure because DEP varies from one location to another. Even if elemental carbon (a common marker for DEP) were used, there are other combustion sources that would be incorrectly counted as DEP. OEHHA assumes without supporting evidence that "diesel exhaust is a significant contributor [to ambient PM] in many urban areas." OEHHA has not addressed the meaning of "significant contribution" of diesel PM to total ambient PM. A study of 3 California locations estimated that diesel PM comprised from 8-12% of total PM based on dispersion modeling and emission data from 1982 (Kleeman et al., 1999). The current proportion of diesel PM in ambient air is likely to be different than in the past, with some evidence that the levels and proportions are decreasing. The proportion of diesel PM is not a constant but varies within and between cities. *Therefore, the exposure-response relationships estimated*

for PM_{10} or $PM_{2.5}$ or sulfate or any other exposure metric will not reliably represent a valid association for diesel PM. It is not clear that a contribution of less than 10% of ambient PM is biologically significant and sufficient to cause the exacerbation of asthma and respiratory effects being attributed to this particulate source.

- Some of the observed associations are not with PM_{10} and in some studies PM_{10} is not even being measured, which makes it problematic to use the results to test the DEP hypothesis.

For example Thurston et al. (1997) did not measure PM_{10}. Associations were observed with ozone and sulfate, and the likely concentration of DEP is below the threshold of 10 ug/m^3 sulfate in this study. Burnett et al. (1994) measured ozone and sulfate but not PM_{10} or $PM_{2.5}$. OEHHA incorrectly asserts that the association of hospital admissions was with PM_{10}, which was not measured. Bobak and Leon (1999) measured district levels of TSP(estimated as 80% PM_{10}), SO_2 and NO_x. Since DEP is submicron in size the better exposure metric among those available is $PM_{2.5}$>PM_{10}>TSP.

- Associations are sometimes observed with pollutants such as ozone or other pollutants other than PM_{10} or $PM_{2.5}$. In these instances it is inappropriate to assume the adverse effects are due to DEP.

For example, Thurston et al. (1997) concluded the most consistent effects were associated with ozone, although they suggested fine PM (sulfate) might also play a role. But neither sulfate nor ozone has been identified as a suitable surrogate for DEP (Winer and Busby, 1995). Delfino et al. (1997) found slightly stronger associations with ozone (RR=1.22) than with PM_{10} (RR=1.16) or $PM_{2.5}$ (RR=1.12). Bobak and Leon (1999) reported a significant RR of 1.10 (1.01-1.20) of SO2 with low birthweight infants, but no association with TSP (RR=1.03: 0.95-1.11).

- Traffic density or distance from busy roads is also not a pure measure of diesel exposure. In general there is a lack of objective quantitative measure of any pollutant. All traffic is often counted without regard to diesel Vs gasoline engines. Strachan (1996) comments on some of the problems associated with interpreting studies of asthma and pollution from motor

vehicles using proximity to major roads and/or traffic density as the exposure metric. The pollutants of major concern have been PM and NO_x. Both pollutants decrease with distance from the source, but the decline beyond 20 meters is small. Imputing traffic exposure from place of residence is problematic as home represents only a small part of daily exposure to ambient air and indoor sources (e.g. cooking fuels, environmental tobacco smoke) are more important sources of exposure to NO_x and PM.

For example, Wjst et al. (1993) estimated car traffic from census data but NO2 concentrations were not correlated with traffic, correlation with PM was not reported, and there was no estimate of diesel traffic. Edwards et al. (1994) used municipal traffic flow data and distance from roads but could not distinguish between diesel and gasoline engine traffic. Van Vliet et al. (1997) used distance of the home from the freeway and traffic counts of diesel and car traffic collected 2-years before the study to measure exposure. There were no concentration gradients for PM_{10} or $PM_{2.5}$ and concentrations were only poorly correlated with diesel traffic. There were slight gradients for NO_2 and black smoke (BS). NO_2 showed some correlation with total traffic and BS with diesel traffic. And the gradients for NO_2 and BS were much smaller than the 4-fold differences between classrooms. Oosterlee et al. (1996) used a mathematical model to estimate NO_2 concentrations, but there was no estimate of the contribution of diesels or DEP to the atmosphere or to personal exposure of the study subjects.

Response: As indicated in this comment, there are many studies (in fact, hundreds) that report associations between ambient concentrations of PM, measured at fixed site monitors, and a suite of health effects, including mortality and hospitalization for cardiovascular and pulmonary disease. By necessity, these studies typically use exposure data collected at central monitoring stations, or monitors established expressly for a particular epidemiologic study. Given the sample sizes necessary for the epidemiologic studies, it is not financially practical to measure the personal exposure of all subjects in a given study. In addition, the attainment of ambient standards is based on readings at these monitor sites. Therefore, it is reasonable to examine whether changes in these readings are correlated with carefully documented adverse health outcomes. Some studies have adjusted the fixed site readings for time-activity patterns and indoor penetration in order to improve the exposure estimates. In addition, a separate set of

studies have confirmed the high outdoor to indoor penetration rates (approaching unity) of fine particles, including elemental carbon, and the high day-to-day correlation of outdoor and indoor particles over time for a given household. It is well know that random misclassification of exposure would tend to bias the estimates of effect towards the null. Therefore, it is unlikely that the dozens of published studies have all been biased by non-individualized exposure assessment towards finding an effect of PM.

The commenter is referred to the report prepared for the Air Quality Advisory Committee for discussion of individual studies important in delineating the effects of PM and their potential for differential impacts on infants and children. That portion of the report is appended to these responses to comment as Appendix A. Note that this report underwent public comment and peer review and was adopted by the Air Resources Board during the prioritization of criteria air pollutants for review of the standards for adequacy to protect infants and children.

Diesel exhaust particulate matter is part and parcel of ambient PM10. There are many studies showing impacts of both PM 10 and now PM 2.5. The science at this point is inadequate to attribute all the effects to one or other size fraction of PM, and existing studies show effects of both size fractions. The assertion that PM from diesel engines could not be involved in any of the cardiopulmonary responses associated with PM10 is illogical.

Comment 7:

B. Inconsistent Results

OHHEA indicates that non-cancer "effects of diesel exhaust are likely due to the presence of particles in the exhaust." OHHEA then asserts that ambient PM (to which diesel exhaust is said to be a significant contributor) has been associated with adverse effects on the respiratory system (e.g. irritation especially cough, phlegm), declines in lung function, increased hospital admissions, and increased hospital admissions, increased mortality during severe air pollution episodes. These effects are particularly seen for asthmatics, those with existing disease, and the elderly. And because asthma is more common among children than adults, the effects of air pollution on asthma "put more children at higher risk of PM health effects than adults."

None of the data presented by OHHEA can be inferred as a direct test of the hypothesis that DEP is causing the adverse health effects since there are no measurements of DEP or markers of DEP. Even is one accepts the invitation, some results are not consistent with the hypothesis that ambient PM is the major cause of some effect.

- Stronger associations are sometimes seen with non-PM pollutants. Thurston et al. (1997) concluded that the most consistent associations of asthma exacerbations among asthmatic children at camp were with ozone, with only a possible role for sulfate. Ostro et al. (1995) did not find associations of symptoms such as cough and wheeze, use of asthma medication, or reductions in peak flow associated with PM_{10} among African-American asthmatic children in Los Angeles. Delfino et al. (1997) reported that ozone was more strongly associated with respiratory hospital admissions than was PM_{10} and $PM_{2.5}$. Burnett et al. (1994) reported that ozone was a stronger predictor of respiratory hospital admissions than was sulfate.

- Children (or lower VS normal birthweight infants) are not consistently the most susceptible population. Delfino et al. (1997) found that children were not the most susceptible population as children aged 2-18 showed no association with any pollutant, and infants < 2-years showed a weak association only with H+. The strongest associations were with adults >65 years of age and the most important pollutant was ozone rather than PM_{10}, $PM_{2.5}$, or sulfate. OEHHA invites one to infer from the data of Burnett et al. (1994) that children are at highest risk because the "largest percent increase in hospital admissions associated with PM_{10} [was] in the 0-1 year old age group of children in Ontario." But a more critical examination of the Burnett et al. (1994) suggests there are no reasonable differences between age groups. The highest percentage of hospital admissions were among the 0-1 year age group (13%, $p<0.05$), but the most significant association was among the 35-64 year age group (9.8%, $p<0.001$). In all the 168 acute care hospitals in Ontario the number of admissions each day attributed to 50 ppb ozone + 5.3 ug/m^3 sulfate was 0.68 admissions/day for 0-1 year infants, 1.25/day for ages 2-34, 0.86/day for ages 35-64 and 0.36/day for ages 65+. There is a 3.2% difference (or 0.18 admissions/day) between the "susceptible" 0-1 year infants and the most robust (presumably) part of the total population (ages 35-64). These differences seem too

small to provide much support for the hypothesis of differences in risk by age. The study by Woodruff et al. (1997) lacks internal consistency in that the most susceptible low birthweight (LBW) infants showed a nonsignificant association with respiratory deaths (RR-1.05; 0.91-1.22), while the less susceptible normal birthweight (NBW) infants show a elevated risks of 1.12 (1.07-1.17) for sudden infant death (SIDS) and 1.20 (1.06-1.36) increased risk for respiratory deaths.

- Associations are not consistently observed with reduced lung function or relevant symptoms. Wjst et al. (1993) did not show significant associations between traffic density and reductions in important measures of lung function (FVC, FEV, peak flow), airway reactivity, or with the most relevant respiratory symptoms (asthma, allergic rhinitis, recurrent shortness of breath, coughing).

- Girls show asthma-related effects, but boys do not. This is an intriguing but inconsistent finding which is unexpected since boys have higher asthma rates than girls and spend more time outdoors. But OEHHA does not explain how these findings are consistent with the hypothesis that children are the subpopulation most susceptible to DEP or PM_{10}.

Van Vliet et al. (1995) reported that girls living within 100 meters of freeway showed significant 2.5-fold and 3-fold increased risks of chronic cough and wheeze respectively, nonsignificant 2.3-fold increased risk of rhinitis, and no increased risks of asthma attacks or bronchitis. For boys there were no associations for any of these exposures or symptoms as RRs were generally close to 1.0. Brunekreef et al. (1997) reported similar results for lung function with regard to associations with girls but not boys. Oosterlee et al. (1996) showed significant associations between some respiratory symptoms and traffic density for girls, but not for boys or adults. For girls there were significant ORs of 4.4 (1.4-13.6) for the symptom 'ever wheeze,' 5.3 (1.1-25) for wheeze in past year, 4.8 (1.3-18) for ever having an attack of dyspnea with wheeze, 15.8 (1.4-174) for attacks of dyspnea with wheeze in the past year, and 2.9 (1.1-7.9) for increased use respiratory medication. For boys the ORs were near or below the null: 1.2 (0.4-3.7), 0.7 (0.2-2.5), 0.9 (0.2-3.2), 0.4 (0.1-2.6), and 1.3 (0.4-4.4) respectively. The only significant OR for adults was 1.8 (1.1-3.0) for dyspnea occasionally during walking.

Response: For several reasons, ambient PM is not always significantly associated with an adverse health effect. It may be due to poor measurement of exposure or health effect, poor study design, inexact control of potential confounders, omitted variables in the regression models, averting behavior on the part of individuals, or because certain individuals are not sensitive to the effects of particles. Given that the effect per microgram of PM is relatively small, it is not surprising that some studies do not find an effect. What is surprising, in fact, is that so many studies do find an effect of PM on a constellation of outcomes ranging from mortality and hospitalization to asthma exacerbation and minor respiratory symptoms. These small risks, multiplied by wide exposure of the population, result in significant impacts on both children and adults. While individual studies have flaws, as indicated by the commenter, the depth of evidence, taken as a whole, provide strong support for the hypothesis that exposure to PM is associated with adverse health. While DEP has not been explicitly measured in these studies, it is reasonable to assume that as a constituent of fine particulate mass, it is likely to have the same effect as other fine particles.

Comment 8:

C. Confounding.

Confounding at the individual-level (e.g. SES, indoor environment) may not be adequate in community cross-sectional and case control studies and particularly where traffic density is the exposure metric.

Woodruff et al. (1997) raise the issue of confounding from uncontrolled risk factors for which they had no information (e.g., environmental tobacco smoke). They reasoned that the lack of control on additional risk factors was not important because in the Six Cities (Dockery et al., 1993) and ACS (Pope et al., 1995) cohorts additional risk factors had not significantly altered the relationships between $PM_{2.5}$ and adult mortality. This reason is not adequate justification for concluding such risk factors are not confounding the association in the Woodruff et al. study.

Some individual-level risk factors were important in the Six Cities and ACS cohort studies. In the HEI reanalysis of the ACS cohort (Krewski et al., 2000) adjustments for potentially confounding factors reduced RRs to nonsignificance. All cause mortality was reduced to 1.05 (0.85-1.30) after regional adjustment and including relative humidity and SO_2 in the model. Cardiopulmonary mortality was reduced to 1.13 (0.91-1.40) after regional adjustment and including income, poverty, income disparity, unemployment, and education in the model. Education clearly modified the air pollution-mortality associations in both the Six Cities and ACS cohorts. Individuals who had not completed high school had the highest risk of mortality while individuals who had completed high school "did not appear to have had increased risk." The reanalysis team thought education was a marker for a more complex set of socioeconomic variables that impact upon the level of risk. Based on the results of the extensive reanalysis by Krewski et al. (2000) that went beyond that of the original authors, it seems likely that the socioeconomic status (SES) may not be under adequate control in studies where comparisons are made between groups. For example, it is not clear in the study by Woodruff et al. (1997) that maternal education provides adequate adjustment for a set of socioeconomic variables. The question of adequate adjustment for SES as well as other factors in the indoor environment applies to basically all the epidemiological studies except the time-series studies. When the RRs are small (< 2-fold say) the inadequate control of confounding becomes increasingly important.

Socioeconomic status (SES) is a potentially major confounding factor that has not always been considered in the studies using traffic density as an exposure variable or other studies where subgroups of the population are being compared. SES becomes a confounder because lower SES status is a risk factor for poor respiratory health (including asthma symptoms) and is also associated with living closer to roadways and increased indoor exposure. For example, environmental tobacco smoke (ETS), particularly maternal smoking, is more common among those with lower SES. It is also associated with the development of asthma, with increased use of asthma medications and earlier onset of asthma, with increased prevalence of cough, phlegm, shortness of breath, wheeze, asthma and reduced lung function (FEV, FVC), and with current asthma (Agabiti et al., 1999; Weitzman et al., 1990; Cook and Strachan, 1997; Burchfiel et al., 1986).

van Vliet et al. (1997) comment that the findings from Edwards et al. (1994) are limited because no information on potential confounders was available. And van Vliet et al. (1997) also reported that the associations in their study were "mainly restricted to the children of intermediate and low SES." Strachan (1996) suggests that when there are significant associations between wheezing and traffic density the prevalence varies by a factor too great to be readily explained by the subtle differences in concentrations related to traffic density. This argues "for a cautious interpretation and careful consideration of possible confounding factors and reporting artifacts."

- Unadjusted spatial gradients in national data lead to confounded associations (i.e., infant mortality).

As noted in the previous paragraph Krewski et al. (2000) found spatial trends to be an important confounder in the ACS cohort mortality study of Pope et al (1995). Woodruff et al (1997) did not adjust for geographic variations in mortality. Based on the Krewski et al (2000) the new results from the Six Cities and ACS studies are not consistent with Woodruff et al. (1997) as these authors suggested. The Krewski et al. (2000) reanalysis suggests that Woodruff et al. (1997) did not control for important covariates (e.g. spatial covariates) that could change (reduce to nonsignificance) their risk estimates.

Lipfert et al (2000) explored the associations of ambient PM and a range of categories of infant mortality. Their results are consistent with the idea that air quality is one of several possible indicators describing a geographic area. Lipfert et al (2000) show that PM10-associated infant mortality is independent of the likelihood of exposure in that the coefficient for neonatal deaths of LBW infants (much less likely to be exposed) is not significantly different from the coefficient for postneonatal deaths on NBE infants (more likely to be exposed). They show strong positive associations of PM10 with SIDS that are quite sensitive to geographic. Even stronger negative associations with sulfate were observed. Lipfert et al (2000) conclude that these results provide "no support for the hypothesis that SIDS is associated with outdoor ambient concentrations of generic fine particles," which is contrary to the conclusion of Woodruff et al. Epidemiologic studies with geographic gradients such as those for infant mortality can result in

misleading results unless a "broad range of alternative hypotheses and candidate confounders is not also investigated" (Lipfert et al, 2000).

Response: OEHHA thanks the commenter for pointing out the difficulties in accounting for confounding factors. We will be discussing these comments and looking into the issues as we revise the document. The commenter is referred to the report prepared for the Air Quality Advisory Committee (appended as Appendix A to these responses) for discussion of individual studies important in delineating the effects of PM and their potential for differential impacts on infants and children. Note that this report underwent public comment and peer review and was adopted by the Air Resources Board during the prioritization of criteria air pollutants for review of the standards for adequacy to protect infants and children.

Comment 9:

D. Factual Errors

The authors of OEHHA have misrepresented or misinterpreted the results of several of the studies that were cited.

- OEHHA reported that Thurston et al. (1997) said that medication use for asthmatic children at summer camp "was a metric of severe air pollution effects associated with sulfate (a measure of particle pollution)." Thurston et al. (1997) indicated that for medication use sulfate showed a stronger association than ozone, but this association "warrants further investigation, [and] these various exploratory multipollutant analyses generally indicate that ozone is the air pollutant most strongly and consistently associated with adverse health effects in this population of children with asthma." And the association with sulfate was "more dependent on a single extreme day that was high for all the pollutants considered (as well as for temperature)" and the sulfate association "may be indicative of a fine particle effect."

- OEHHA reported that Ostro et al. (1995) found significant associations between PM_{10} and asthma symptoms in 7-12 year old Los Angeles residents." Ostro et al. (1995) measured PM_{10}, ozone, NO_2, SO_2 as pollution exposure variables. Response variables included "six binary response variables indicating daily symptoms: the prevalence of cough, shortness of breath and wheeze, and the likelihood of a new episode of any of these three asthma symptoms, that might extend over several days." "Of the pollutants, PM_{10} and ozone were associated with shortness of breath but not with any other symptom and was the only symptom examined in subsequent models." For the subsample of the population with moderate-severe asthma and in the individual-level analysis, the "beginning of an incident attack (or episode) of shortness of breath was associated with ozone, but not PM_{10}" "The biological plausibility of the consistent statistical relationship between PM_{10}, ozone, and reported shortness of breath would be strengthened by finding similar associations with wheezing." And since concentrations of PM_{10} and ozone were correlated, it "is difficult to attribute these effects solely to one pollutant."

- OEHHA described Delfino et al. (1997) as having found ""significant association between PM_{10} and bronchodilator use in asthmatic children." However, Delfino et al. (1997) is a time-series study of respiratory and nonrespiratory illness emergency room visits for all ages. It is not a study of asthmatic children and there is no measure of bronchodilator use.

- OEHHA indicated that Bobak and Leon (1999) had "linked infant mortality in the Czech Republic to long-term exposures to PM." Bobak and Leon (1999) conducted an ecological study using aggregated response data on low birthweight and stillbirths, which were linked to concentrations of total suspended particulate (TSP), SO_2, and NO_x. PM_{10} was not associated with infant mortality and air pollution explained very little of variance in mortality. Neither TSP nor NO_x were associated with low birthweight infants as the RRs were 1.03 (0.95-1.11) and 0.99 (0.89-1.10) respectively. The socioeconomic variables explained 50% of the variability in the data, while the pollutants explained only 2% of the variability. There were no significant associations of infant mortality and pollution, with adjusted OR of 0.92 (0.74-1.15) for TSP, 0.90 (0.70-1.16) for SO_2 and 1.21 (0.89-1.64) for NO_x. However the statistical model without pollutants explained only 5% of the variability and the statistical

model with pollutants explained even less (4%), indicating pollutants contributed essentially no information toward explaining variability in the infant mortality data.

- OEHHA said Wjst et al. (1993) reported decreases in lung function that were associated with increased traffic density. However, the OEHHA description of the findings from Wjst et al. (1993) does not indicate that there were no significant decreases in Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), or MEF75 (Maximal expiratory flow at 75% of FVC). MEF25 and MEF50 were significant. The abstract indicated peak expiratory flow rate (PEFR) was significantly reduced by 0.71% (95% confidence interval 1.08% to 0.33%). Since the upper 95% confidence level is positive (indicating an improvement in PEFR), it would appear PEFR is not associated with traffic density. Also, there was no increased airway reactivity as measured by cold air challenge. Overall these results do not show a consistent association of reduced lung function associated with traffic density. FEV1 is the most reproducible measure of both large and small airway obstruction and is an indicator of morbidity and mortality. Twitchy airways is a characteristic asthmatic response. So the observed effects do not suggest significant changes in the two most important measures of obstruction and restriction, or in airway reactivity.

- OEHHA does not mention the findings of associations with girls but not boys (van Vliet et al., 1997; Brunekreef et al., 1997; Oosterlee et al., 1996) and how this important inconsistency might modify their characterization of these studies as indicating respiratory effects of diesel PM.

Response: OEHHA disagrees with many of the commenter's interpretation . However, we will be evaluating these comments during the revision of our draft document and will correct any mistakes then. The commenter is referred to the report prepared for the Air Quality Advisory Committee for discussion of individual studies important in delineating the effects of PM and their potential for differential impacts on infants and children (Appendix A in the back of these responses). Note that this report underwent public comment and peer review and was adopted by the Air Resources Board during the prioritization of criteria air pollutants for review of the standards for adequacy to protect infants and children.

Thurston prepared the report we utilized for the ambient air quality standard review for prioritization under SB 25. Thus, Thurston himself described the results of Thurston et al. 1997. As noted below, it is highly likely that there are interactions among pollutants that influence the measured outcomes in epidemiology studies. This does not mean there is no particle effect.

It is true with many air pollution epidemiology studies that it is difficult to ascribe effects a single pollutant. In fact, it may be that there are interactions among the pollutants that result in the measured effects. However, despite this, and contrary to the assertion in the comment, there are indications in Ostro et al., 1995 that PM was associated with shortness of breath in the children in the study. In addition, Ostro et al., 2001, a larger study of asthmatic children, clearly shows an independent effect of PM10 on exacerbation of asthma in children in Los Angeles.

As regards the comment on Bobak and Leon (1999), total suspended particles, not PM10, were significantly associated with postneonatal respiratory mortality (OR 1.95; 1.09-3.50 per 50ug/m3 increase in TSP), as was sulfur dioxide. These authors did not measure PM10. Thus the comment that PM10 was not associated with mortality is a bit misleading. Furthermore, OEHHA staff cannot find the purported OR ascribed in the comment to the Bobak and Leon (1999) investigation in the original paper. Perhaps the commenter is referring to a different study.

The point regarding the Delfino et al, 1997 study is a case of mistaken citation. This will be corrected in the revision to the document.

The commenter is correct as regards the Wjst et al., 1993 study in that there were no significant changes in FVC, FEV1, and MEF75 in children in school districts by traffic density. However, the decreases in PEFR were significant at $p<0.001$. In addition decreases in MEF25 and MEF 50 were significant with p values of 0.002 and 0.009, respectively. These associations were significant after adjusting for exposure to ETS, use of gas or coal for cooking, sex, and parental asthma. In addition, recurrent dyspnea was significantly elevated in children in the highest tertile of traffic density. The sample size was large (over 5000 children). Recurrent wheezing and

recurrent dyspnea also reached statistical significance by traffic density in these children. These latter symptoms are characteristic of asthma.

The interesting difference between girls and boys noted in the traffic studies is just that, interesting. It does not decrease the relevance of the findings in girls. Oosterlee et al. 1996 report associations between living on a busy roadway and a number of measures of respiratory health in girls: OR for wheeze 4.4; 95% CI 1.4-13.6 ; OR for respiratory medication use 2.9; 95% CI 1.1 – 7.9; OR for attacks of dyspnea with wheeze in last year 15.8, 95% CI 1.4-174.4 after adjusting for confounding by age, education of the mother, passive smoking, presence of unvented gas fired appliances, dampness, pets, and number in household. Out of 10 symptoms, only one (occasional dyspnea) was significantly associated in adults with living on a busy roadway. Similarly, van Vliet et al. found significant associations in girls between chronic cough (OR 2.45; 95% CI1.16-5.16) and wheeze (OR 3.05; 95% CI1.11-8.41) and residing close to a freeway. .

Comment 10:

E. Additional Studies

A cursory search of the literature identified 3 additional studies related to traffic density. While these studies have many of the same problems as the studies referenced by OEHHA, they tend to show a lack of associations rather than positive associations. A fourth study of infant mortality in the U.S. This study by Lipfert et al (2000) provides a different interpretation of the study by Woodruff et al (1997) and suggests that other factors related to geographic and individual-level risk factors rather than air pollution (including PM10, and therefore DEP) are causally associated with infant mortality.

- Venn et al. (2000) found that traffic activity around primary and secondary schools was not a major determinant of wheeze or asthma symptoms in children. Ecological analysis showed substantial variation in wheeze between schools that did not seem to be due to road traffic in

the individual-level analysis. Road traffic was directly measured and adjustments for factors in the home environment (e.g. social class, parental smoking) were attempted.

- English et al. (1999) used geographic information systems (GIS) and pollutant dispersion models to estimate traffic flow. The number of medical care visits for asthma showed no statistically significant associations with traffic flow although heavy exposure may have increased the risk of medical care visits for girls (but not boys). The authors interpret their data as suggestive that heavy exposure to traffic might exacerbate symptoms in those with asthma, but found no relationship with the initiation of asthma.

- Livingstone et al. (1996) conducted a case control study of hospital admissions for asthma in east London. There were no associations with traffic for either children or adults (Livingstone et al., 1996). Cases had a slightly higher but nonsignificant deprivation score suggesting somewhat lower SES. Adjustments were made for sex, practice and age. There was no increase in risk of asthma associated with living close to busy roads for adults or children with the dichotomous exposure metric of less than 150 meters from a busy road Vs greater than 150 meters. There was also no association when residence was a continuous variable. The OR was 1.0 (0.84-1.19) for those age 16-64 and 0.96 (0.78-1.22) for those age 2-15. The similarity in OR for adults and children is suggestive of no increased risk of children compared to adults in this population.

- Lipfert et al (2000) linked birth and death records with annual county averages of PM10, Co, SO2, sulfate, and nonsulfate PM10 to explore associations between infant mortality and environmental factors in the U.S. Information on potential confounders included personal data on the mother (i.e., age, adequacy of prenatal care, smoking and education) and ecologic variables (e.g., elevation, climate, physicians/capita, median income, racial and ethnic distribution, unemployment, and population density). Infant deaths were examined by age (neonatal and postneonatal), by birth weight, and by specific causes within these categories with special emphasis on sudden infant syndrome (SIDS). The model of Woodruff et al (1997) was used as a point of departure, and the results from the two datasets were similar. Lipfert et al (2000) derived some results not generally observed before.

+ There were similar relationships of PM10 with all categories of infant mortality (except some higher risks for infants with smoking mothers).

+ There were strong negative associations of sulfate with SIDS mortality, all birth weights and smoking statuses, postneonatal mortality and normal birth weight deaths. There were positive associations with neonatal mortality and low birth weight deaths.

+ The positive associations between SIDS and PM10 and the negative associations with sulfate and SO2 are due to the east-west gradient in SIDS. Neither the negative nor the positive associations should be "considered as evidence of a causal relationship between SIDS and air quality."

On the basis of these disparate results and consideration of what air quality is actually measuring, Lipfert et al (2000) consider two alternative paradigms.

1. Air quality is a surrogate measure of actual exposure. According to this paradigm significant associations might be causal.
2. Air quality is one of several geographic descriptors of the places where air quality measurements were taken. According to this paradigm any causal interpretation requires "elimination of all the other site characteristics that might be spatially correlated with air quality (including other air pollutants).

Lipfert et al (2000) conclude that the first paradigm does not fit the data in this study because the associations of PM10 with various categories of infant deaths are independent of the likelihood of exposure. Evidence from the literature is consistent with this interpretation.

- There were no significant associations between SIDS and residence near cokeworks despite higher SES deprivation pollution levels (Dolk et al, 2000).
- The same variables were significant for SIDS and non-SIDS deaths on the state-level and were associated with the east-west gradient (Spiers et al, 1974).
- Higher SIDS on weekends (higher pollution) than during the week (lower pollution, infants at home less due to daycare) in a number of industrialized countries suggests air quality is an unlikely common factor (e.g., Spiers et al, 1999; Hendry RA, 1981; Mathers, 1983; Mitchell et al, 1988; Kaada et al, 1990).

Lipfert et al (2000) conclude that these data provide no support for the hypothesis that SIDS and other categories of infant mortality are associated with ambient PM10 or PM2.5. Epidemiologic study results can be confounded by geographic patterns and can be misleading if alternative hypothesis and a broad range of confounders are not also investigated. A thorough exploration of various predictors is necessary to preclude implicating the wrong agent(s). The results of Woodruff et al (1997) by this analysis are likely due to the geographic gradient resulting in a false positive finding.

Response: OEHHA thanks the commenter for pointing out the additional studies. We will be considering these comments during revision of the draft document. As noted in response to previous comments, the brief summary provided in the prioritization document was intended only to identify a selection of studies that OEHHA felt might have some bearing on the possibility of differential effects on infants and children. Furthermore, it is very often the case that some epidemiology studies trying to measure an outcome are positive while others are negative. The traffic studies cited in the OEHHA document are well-conducted studies with positive findings. A more detailed evaluation of those effects specifically related to PM appears in the report prepared for the Air Quality Advisory Committee, to which the commenter is referred for discussion of individual studies (Appendix A in the back of these responses). Note that this report underwent public comment and peer review and was adopted by the Air Resources Board during the prioritization of criteria air pollutants for review of the standards for adequacy to protect infants and children.

Comment 11: IMMUNOLOGICAL EFFECTS. Several studies are cited in support of the hypothesis that diesel PM enhances allergic responses to allergens, and that DEPs could induce immunological allergic reactions as well as localized inflammatory responses in humans.

These are experimental studies, either in vivo or in vitro. It is not appropriate to extrapolate the results to the general population. The in vivo studies instilled an excessive concentration of DEP in the nose. Extrapolation is inappropriate since the nose is not the major deposition and the dose is excessive and atypical of even excessive ambient concentrations. The in vitro studies extracted polyaromatics (PAHs) from DEP using an organic solvent rather than lung surfactant.

Thus PAHs could have been extracted that are not normally bioavailable. Whether cells in culture respond as cells in vivo is not reported, and whether the doses to cells in culture is similar to cell in vivo is unknown.

Response: Extrapolation of results from experimental studies to the general population is part of the foundation of scientific risk assessment. The studies cited in the diesel exhaust prioritization document (Diaz-Sanchez *et al*., 1994, 1996, 1997; Terada *et al*., 1997, Takenaka *et al*., 1995) indicate that the exacerbation of asthma by diesel exhaust is due specifically to a modulation of the immune system, and not because of a general irritant effect. It should also be noted that acute healthy adult human exposures to concentrations of diesel exhaust particulate matter (300 $\mu g/m^3$) approximately one order of magnitude greater than peak diesel exhaust concentrations noted near freeways demonstrated a marked leukocytic airway infiltration accompanied by enhanced chemokine and cytokine production (Salvi *et al*., 2000) Since the prevalence of asthma is much higher among children than among adults (CDC, 1996a,b), exacerbation of asthma by diesel exhaust will put more children at higher risk of adverse health effects than adults.

The studies cited above were designed to determine the mechanisms by which diesel exhaust particulate matter modulates immune system response. With regard to the studies performed by Diaz-Sanchez et al. (1994, 1996, 1997), there is no reason to believe that a bolus dose of diesel exhaust particulate matter would have mechanistically different immune system effects compared to the same dose spread out over a period of time. The studies by Terada et al. (1997) and Takenaka et al. (1995) are mechanistic studies which support the findings of Diaz-Sanchez et al., and are useful in determining how diesel exhaust exacerbates asthma. They are not being used in the present context as the basis of a quantitative risk assessment.

Finally, the draft document is not a quantitative risk assessment, but rather a hazard identification document. Issues of dose-extrapolation are not being addressed in the prioritization of TACs for listing under SB 25.

Comment 12: REPRODUCTIVE EFFECTS. In a study examining the effects of DEP on male reproductive function, mice were exposed 12 hour/day to high levels (30, 100, 300, or 3000 ug/m^3) DEP for 6 months. Histopathological changes in Leydig cells were noted at the three higher dose levels. A NOAEL of 30 ug/m^3 was reported (Yoshida et al., 1999). Since this level is 10-30 times the level of DEP found in ambient air, it is difficult to determine the practical significance of the finding. One conclusion would be that at current exposure levels, DEP presents no hazard to male reproduction.

The review cites another study in rats where developmental toxicity as a result of maternal exposure has been reported (Watanabe and Kurita, 2001). The authors conclude that the effects observed were the result of "exposure-induced changes in the fetus and its interaction with the maternal endocrine system, rather than maternal toxicity or adaptation." The review fails to note that the exposure levels used in this experiment were extraordinarily high (5,630 ug/m^3 particulate matter, 4 ppm nitrogen dioxide, 8 ppm nitrogen oxide). At these high exposure levels, it is unclear how the authors can conclude that maternal toxicity is not a major factor in the effects observed. Also, the significance of the findings for ambient exposures, which are over 1000 times lower than those used in the experiment, is very questionable.

Response: The study by Yoshida *et al*. (1999) reported a reproductive NOAEL and LOAEL for diesel exhaust in rats of 30 and 100 µg/m^3, respectively. The LOAEL is only approximately 30-fold higher than the average ambient diesel exhaust concentration in California, and is very close to peak diesel exhaust concentrations measured near California freeways. After considering these facts, along with considerations of interspecies variability (humans may be more sensitive than rats) and intraspecies variability (sensitive human subpopulations may exist), the levels used in the study by Yoshida *et al*. (1999) are very relevant to the general population.

Watanabe and Kurita (2001) did not report maternal toxicity in their study. The exposure levels used in the study by Watanabe and Kurita (2001) are similar to those used in studies of diesel exhaust carcinogenicity. Acute and/or chronic toxicity was not considered to be a confounder in those studies; there is no reason to believe maternal toxicity is a confounder in the study by Watanabe and Kurita (2001). There are always uncertainties inherent in high dose to low dose

extrapolation. These studies are being used in the present context in a hazard identification process, not a risk assessment process, to determine if diesel exhaust has the potential to disproportionately impact the health of infants and children. They are not being used here as the basis of a quantitative risk assessment. In addition, we are not relying heavily on this study as a basis for considering the listing of diesel exhaust particulate under SB 25.

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APPENDICES:

The comments (and Appendices 3, 4 and 5 described below) discuss in detail some non-cancer effects that have generally been studied in the context of investigations of exposure to particulate materials. The relevant literature was reviewed in detail in a recent report prepared by Dr. George D. Thurston, a noted expert in the field, for the Air Quality Advisory Committee (AQAC) as part of its evaluation of criteria pollutants under SB25. This report was reviewed and accepted by the AQAC after a workshop and receipt of public comments, and subsequently approved by the California Air Resources Board. In order to provide a complete response to the comments supplied on this occasion, the section of the report for AQAC dealing with PM exposures is included here as Appendix A to OEHHA's comments.

A: PARTICULATE MATTER AND SULFATE: EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN.

The commenter provided several appendices, which reiterate comments made in the main text of the comments, with additional detail.

The following appendices were supplied:

1: CANCER UNIT RISK*

2: DIESEL EXHAUST AS A LUNG CARCINOGEN*

3: PM STUDIES OF NONCANCER EFFECTS

4: TRAFFIC DENSITY AND RESPIRATORY EFFECTS

5: IMMUNOLOGICAL EFFECTS

* As noted in OEHHA's responses to earlier comments, diesel exhaust (as quantified by DEP measurements) is a carcinogen, based on evidence from epidemiological studies and in animals. The epidemiological data were found suitable for derivation of a unit risk factor. These were the subject of extensive scientific evaluation, public discussion and peer review during the TAC identification process for diesel exhaust. The present process does not invite any discussion or modification of these conclusions.

APPENDIX A:

PARTICULATE MATTER AND SULFATE: EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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California Office of Environmental Health Hazard Assessment

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Abstract

Epidemiological evidence indicates that present-day ambient particulate matter (PM) and/or sulfate air pollution exposures are associated with adverse health effects in children, including that:

Short-term PM and/or sulfate exposures to children are associated with:

- reduced pulmonary function;
- increased respiratory symptoms in asthmatics (e.g., asthma attacks) and non-asthmatics;
- increased incidence of respiratory doctor's visits;
- increased incidence of emergency department (ED) visits and hospital admissions (HA's);
- increased mortality, and;
- especially increased infant morbidity and mortality;

Long-term chronic PM and/or sulfate exposures to children are associated with:

- reduced lung function;
- increased respiratory symptoms; and,
- increased infant mortality, intrauterine growth reduction, or pre-term delivery.

Especially apparent in the many studies examined, and of notable concern, are results indicating much higher risks for children in the neonatal (< 1 month) and post-neonatal (1-12 months) age groups. Furthermore, an examination of key medical visits and hospital admissions studies indicates that the existing Federal and California PM_{10} and $PM_{2.5}$ mass and sulfate ambient air quality standards are not presently sufficiently protective of public health, as significant adverse health impacts have been documented in published studies at mean ambient levels below these standards.

Both biological and physical exposure-related factors enhance the risk to children from PM and sulfate exposures. These risk-enhancing factors include:

- higher PM concentration exposures resulting from children's greater activity levels;
- larger PM doses in children from increased ventilation rates;
- greater doses of ultrafines among children 14-18 years of age;
- enhanced PM doses in children, especially infants, per body weight and lung surface area;
- diminished and developing defense systems in infants;
- higher prevalence of children with asthma than in other age groups;
- larger percentage of children made susceptible by poverty than other age groups; and,
- gas-particle interactions and particle-allergen interactions, potentially making the individual pollutant standards not fully protective to susceptible populations, such as children.

Based on the above insights, it is recommended that future PM research should focus on:

- improved identification of the specific characteristics of PM (e.g., ultrafines, acidity, elemental composition, etc.) that are contributing most to noted PM effects, and quantification of their relative roles in PM toxicity;
- further investigation as to whether acute exposures less than one day in length (e.g., 1-hr. daily maximum), or longer multi-day exposures (e.g., 2 or more day average PM), also have health importance, over and above that captured by the 24-hr. PM peak PM concentration measurement;

- further investigations into particle-gas and particle-allergen interactions;
- using both experimental and epidemiological methods, conduct further investigations of apparently larger acute and long-term effects of PM on children, and especially infants.

Table of Contents

I. BACKGROUND

This section briefly summarizes the existing California state and federal ambient standards for particulate matter (PM) and sulfate ($SO_4^{=}$), and the rationale for these standards.

According to California State Code of Regulations Section 39606 (b), the state board shall adopt standards of ambient air quality for each air basin in consideration of the public health, safety, and welfare, including, but not limited to, health, illness, irritation to the senses, aesthetic value, interference with visibility, and effects on the economy. These standards may vary from one air basin to another. Standards relating to health effects are to be based upon the recommendations of the State Department of Health Services. The term "Ambient air quality standards" means specified concentrations and exposure durations of air pollutants that reflect the relationship between the intensity and composition of air pollution to undesirable effects established by the state board or, where applicable, by the federal government. "Air contaminant" or "air pollutant" means any discharge, release, or other propagation into the atmosphere and includes, but is not limited to, smoke, charred paper, dust, soot, grime, carbon, fumes, gases, odors, particulate matter, acids, or any combination thereof.

The present particulate matter (PM) mass-based ambient air quality standard in California is indexed to PM_{10}, which refers to atmospheric particles, solid and liquid, except uncombined water, as measured by a PM_{10} sampler that collects 50 percent of all particles of 10 micrometers (um) aerodynamic diameter, and that collects a declining fraction of particles as their diameter increases and an increasing fraction of particles as their diameter decreases, reflecting the characteristic of lung deposition. Suspended particulate matter (PM_{10}) is to be measured by the size selective inlet high volume (SSI) PM_{10} sampler method in accordance with ARB Method P, as adopted on August 22, 1985, or by an equivalent PM_{10} sampler method, for purposes of monitoring for compliance with the PM_{10} standards.

As noted in Table 1, the State of California, unlike the Federal government, also has an air quality standard that was promulgated in the 1970s for the sulfate portion of PM_{10}. Sulfates are the water soluble fraction of suspended particulate matter containing the sulfate radical ($SO_4^{=}$) including, but not limited to, strong acids and sulfate salts, as measured by AIHL Method No. 61 (Turbidimetric Barium Sulfate) (December 1974, as revised April 1975 and February 1976) or equivalent method. The present sulfate standard is a 24-hour average concentration not

to be exceeded more than once per year. In recognition of an inability to discern a threshold at and below which no effects can occur from exposure to this pollutant, this standard is set at a "Critical Harm" level.

Currently, most of the state is in non-attainment with the PM10 standard. The PM_{10} air quality levels dropped from a statewide average of approximately 80 ug/m^3 in 1988 to about 50 ug/m^3 in 1995 and 1996, but rose again to almost 60 ug/m^3 in 1997 (CARB, 1999). State average annual maximum sulfate concentrations dropped by about half between 1980 and 1990 (from about 60 ug/m^3 to about 30 ug/m^3), and have remained fairly stable since that time. Peak summer sulfate in the LA Basin in 1996 was about 17 ug/m^3, and for the last 10 years the mean summer 24-hour concentrations were less than 8 ug/m^3. Thus, typical concentrations are now below the existing sulfate standard, but this is not the case for PM_{10}.

The United States Environmental Protection Agency ("EPA") also recognized the adverse health effects of small particulate pollution as early as 1987 when, pursuant to its authority under the Clean Air Act, it promulgated a National Ambient Air Quality Standard ("NAAQS") for particulate matter that is 10 micrometers in diameter or smaller (PM_{10}). The NAAQS promulgated by EPA are required for certain air pollutants "that may reasonably be anticipated to endanger public health and welfare." The NAAQS' air criteria must be "requisite to protect the public health" with an "adequate margin of safety." Under the particulate matter NAAQS, states must reduce PM_{10} concentrations in their ambient atmosphere to no more than 50 micrograms per cubic meter on an annual average basis, and to no more than 150 micrograms per cubic meter on an average 24-hour period. Prior to 1987, EPA's particulate NAAQS had only regulated total suspended particulate matter. Its focus in 1987 on smaller particles -- that is, 10 micrometers or less -- resulted from increasing scientific evidence that human inhalation of smaller particles had more serious respiratory effects than larger particles.

Table 1. Present California Ambient Air Quality Standards for Particulate Matter and Sulfates
(Source: California State Code of Regulations)

Substance	Concentration and Methods	Duration of Averaging Periods	Most Relevant Effects	Comments
Suspended Particulate Matter (PM_{10})	50 ug/m^3 PM_{10} 30 ug/m^3 PM_{10}	24 hour sample Annual Geometric Mean of 24 hr. Samples	Prevention of excess deaths from short-term exposures and of exacerbation of symptoms in sensitive patients with respiratory disease. Prevention of excess seasonal declines in pulmonary function, especially in children	The standard applies to suspended particulate matter as collected by a PM_{10} sampler, which collects 50% of all particles of 10 um aerodynamic diameter and collects a decreasing fraction of particles as diameter increases, and an increasing fraction as their diameter decreases, reflecting the characteristics of lung deposition.
Sulfates	25 ug/m^3 Total Sulfates AIHL #61 (Turbidimetric Barium Sulfates)	24 hour sample	a. Decreases in ventilatory function b. aggravation of asthmatic symptoms c. Aggravation of cardio-pulmonary diseases d. Vegetative Damage e. Degradation of visibility f. Property damage.	This standard is based as a Critical Harm Level, not a threshold value.

In 1994, the EPA began the process of re-reviewing its particulate matter standards. In 1996, the EPA proposed a new NAAQS for even smaller particles -- those that are 2.5 micrometers in diameter or smaller ($PM_{2.5}$). This new proposed standard was based on an increasing scientific consensus that the current NAAQS for PM_{10} was not sufficiently protective of human health. EPA's scientific review concluded that fine particles, in the 2.5 micrometer and smaller range, penetrate more deeply into the lungs, and may be more likely than coarse particles to contribute to the health effects (e.g., premature mortality and hospital admissions) found in a number of recently published community epidemiological studies at concentrations that extend well below those allowed by the current U.S. PM_{10} standards**.** As EPA stated in its proposed regulation, a greatly expanded body of community epidemiological studies provide "evidence that serious health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM, even in concentrations below current U.S. PM standard" (*Federal Register*, July 18, 1997, Vol. 62, No. 138, pg. 38655).

The recently promulgated NAAQS for $PM_{2.5}$ is 15 micrograms per meter cubed (ug/m^3) based upon the 3-year average of annual arithmetic mean $PM_{2.5}$ concentrations at multiple sites, and 65 ug/m^3 based upon the 3-year average of the 98^{th} percentile of the 24-hour PM_{10} concentration at individual sites. These standards are presently being contested in Federal courts (See: American Trucking Associations, Inc. v. USEPA, 175 F.3d 1027 (D.C. Cir. 1999), modified, 190 F.3d 4 (D.C. Cir. 1999), cert. granted in Browner v. American Trucking

Associations, 120 S. Ct. 2003 (2000) (No. 99-1257), and in American Trucking Associations v. Browner, 120 S. Ct. 2193 (2000) (No. 99-1426)).

II. FACTORS IN PARTICULATE MATTER (PM) AND SULFATE EXPOSURE AND DOSE ASSESSMENT

This section includes, to the extent that information is available, a description of exposure patterns among infants and children that are likely to result in disproportionately high exposures to ambient air pollutants in comparison to the general population.

II.A. PM Concentration Exposures from Children's Activities

Personal activities, such as exercise, cigarette smoking, hobbies, and occupational tasks generate a plume of particles that surround the person generating the particles. Such personal activity sources can exist either indoors or outdoors. These are microscale PM generating activities that primarily influence the exposure of the person performing the activity. Thus, personal activity PM exposure is only measured by a personal monitor carried by the subject, because a stationary monitor located nearby will not measure the high PM concentration generated by that activity. The difference between a personal monitor measurement and an area-representative measurement several meters away is sometimes called a "personal cloud" (Wallace, 1999).

However, personal PM exposure monitoring studies have indicated that personal activities, along with PM generated by personal and indoor sources (e.g., cigarette smoking), can lead to PM indoors and personal exposures to total PM that exceed the concentration of the PM found in the immediate outdoor air or in the local ambient air (Binder et al., 1976; Repace and Lowrey, 1980; Spengler et al., 1980). Fine particles have been found to readily penetrate buildings, but indoor activity adds incrementally to outdoor levels and, frequently, somewhat higher levels of fine particles are observed indoors. Indeed, human activity, such as smoking and cooking, does generate fine particles (<2.5 um); cooking, dusting, vacuuming and general activity can generate coarser particles (>2.5 um), or can resuspend coarse particles that previously had settled out (Litzistorf et al., 1985; Thatcher and Layton, 1995; Abt et al., 1999, 2000).

Children are well documented to have greater activity levels than adults, and therefore are likely to have increased personal exposures, relative to adults, because of an enhanced personal cloud of particles. In recent surveys of the activity patterns of California children and adults

(Wiley et al, 1991a,b), it was found that children 11 years of age and under spend an average of 124 minutes/day doing active sports, walking/hiking, or outdoor recreation, vs. only 21 minutes for adults. In personal exposure studies in the Netherlands, it has been found that, given roughly the same outdoor concentrations, children have a much higher personal PM_{10} exposure than adults (Janssen, et al. 1997, 1998). While children's homes in these studies had a mean outdoor concentration similar to that of adults (41.5 ug/m^3 vs. 38.5 ug/m^3 for adults), children's personal exposures averaged 66.8 ug/m^3 above ambient vs. 26.9 ug/m^3 above ambient for adults. This indicates a much higher "personal cloud" for children than adults. In regressions, personal activity was one of the more important contributors to the children's extra personal exposure concentration, contributing approximately 12 ug/m^3. The children's personal exposure was also some 43 ug/m^3 higher than their time-weighted average of indoor and outdoor concentrations, indicating most of the personal vs. outdoor PM_{10} difference to be due to their personal cloud, rather than generally higher PM_{10} concentrations indoors. Most of these particles are likely to be of indoor origins, however. Thus, PM exposure of a child can be substantially higher than that for adults because of the extra PM that is generated by their own increased activity levels, but the importance of this effect to outdoor air pollution standard setting is limited by the fact that most of these activity generated particles are of indoor origins.

For sulfates, the "personal cloud" phenomenon apparently does not apply as it does for PM mass in general, as sulfate is derived almost exclusively from the outdoors. Indeed, in the PTEAM study (Ozkaynak et al, 1996) conducted in Riverside, CA in 1990, it was found that sulfate concentrations indoors and outdoors were the same, and the researchers concluded that there appeared to be no indoor or personal sources of exposure to sulfate particles. As shown in Figure 1, $SO_4^=$ measured at central monitoring stations in the PTEAM study is closely correlated with $SO_4^=$ as measured by personal exposure monitors. In that figure, the deviations from the line of identity can be largely accounted for by a model that incorporates other known influences. Such close correspondence between personal and outdoor concentrations was not seen for PM_{10} or $PM_{2.5}$ mass concentrations, or for other measured constituents. The close correspondence for $SO_4^=$ can be attributed to it being: a) chemically and physically stable in the air and on sampling filters; b) present primarily as submicrometer-sized particles which penetrate into indoor spaces

efficiently with infiltrating air; c) a secondary aerosol that is distributed quite uniformly across large geographic areas; and d) without common indoor sources.

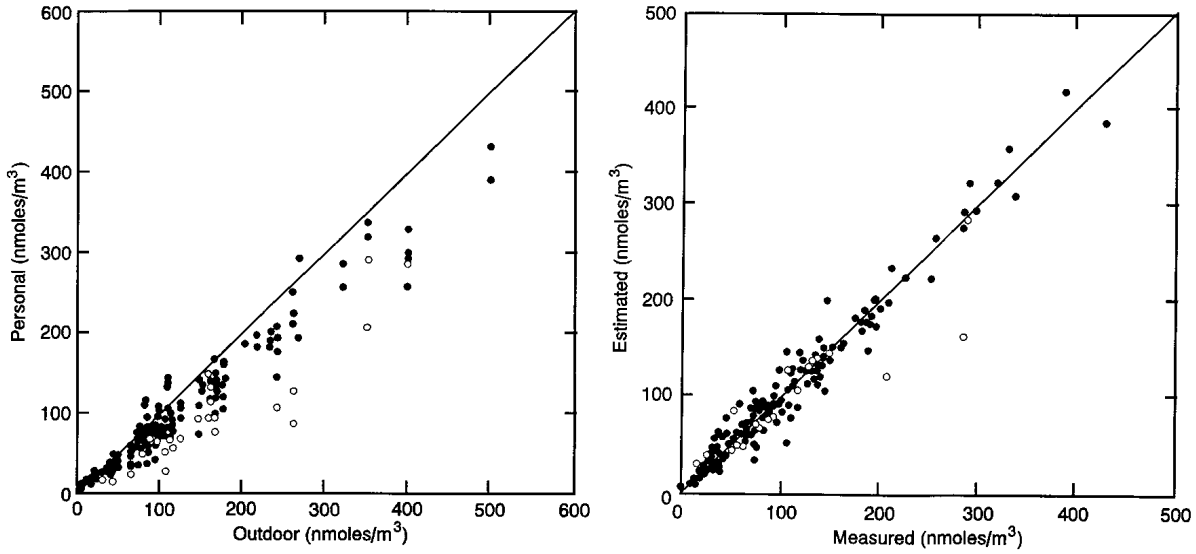

Figure 1. Left Panel: Comparison of personal monitoring data on $SO_4^=$ concentration with temporally coincident central monitoring station $SO_4^=$ in California. (Open circles are air-conditioned residences.)
Right panel: Comparison of measured ambient $SO_4^=$ concentrations with estimated personal $SO_4^=$ exposures based on PTEAM model incorporating known influences on personal exposures.
From: U.S. EPA (1995).

Thus, unlike for PM_{10}, children's personal concentration exposures to sulfates are similar to those of adults, and are well represented by a central site monitors. However, the acidity of sulfates has been found to differ indoors and outdoors, with diminished acidity indoors due to ammonia sources indoors that can convert the acidic sulfates to ammonium sulfate (e.g., see Suh et al, 1994). Thus, while total sulfate exposures are similar for adults and children, the sulfates that children are exposed to are likely more acidic as a result of their greater time spent outdoors, as sulfates are more likely to be in an acidic form outdoors (i.e., as sulfuric acid and/or ammonium bisulfate). Therefore, the greater outdoor time and activity of children outdoors places them at greater risk than adults of exposure to acidic sulfates and acidic gases (e.g., nitric acid).

II.B. Variations in Lung Deposition Fraction in Children vs. Adults

Lung and airway characteristics vary with age, and these variations can change the deposition pattern of inhaled particles. The limited experimental studies available indicate results ranging from no clear dependence of total deposition on age to slightly higher deposition

in children than in adults. Potential deposition differences between children and adults have been assessed to a greater extent using mathematical models, as shown in Figure 2, as derived from the ICRP model (U.S. EPA, 1995). These results indicate that extra-thoracic (ET) deposition (i.e., to the nose, naso-oropharyngeal passages, and larynx) in children is generally higher than in adults, but that tracheo-bronchiolar (TB) and alveolar (A) regional deposition in children may be either higher or lower than the adult, depending upon particle size and age of the child. Overall, available studies do not provide clear evidence for significant differences in deposition fraction between adults and children.

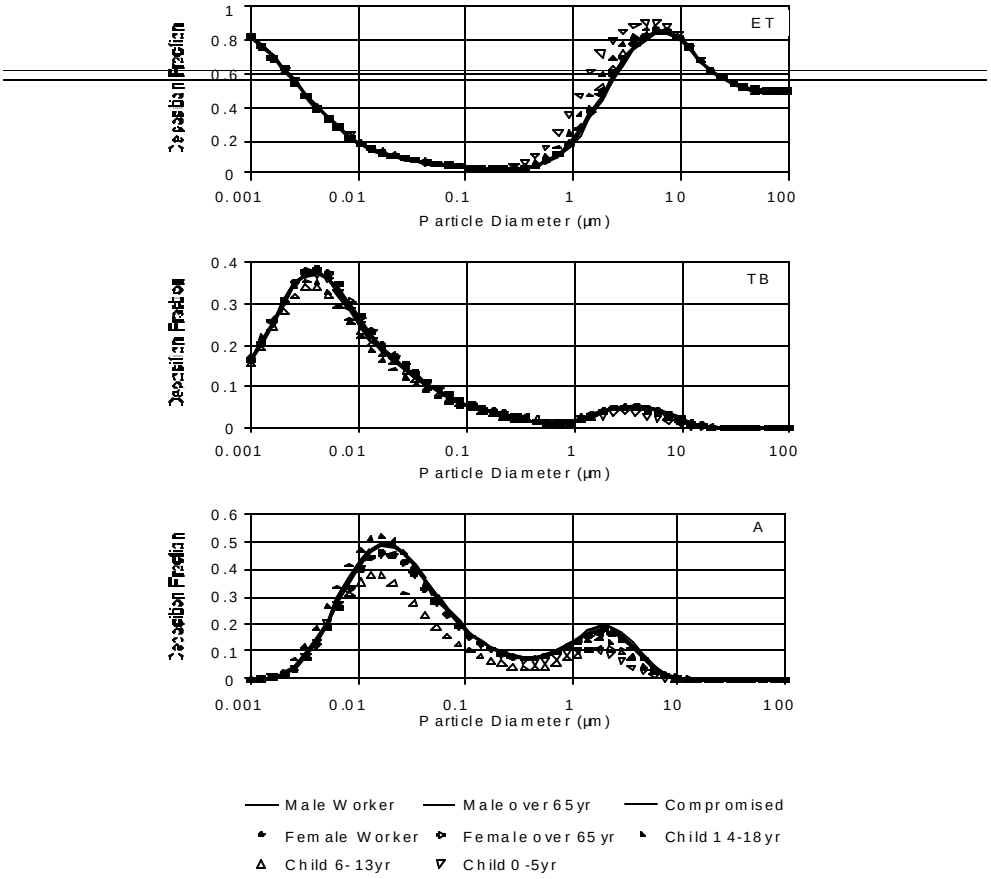

Figure 2. Daily mass particle deposition fraction in each respiratory tract region as predicted by the International Commission on Radiological Protection (ICRP66) (Source: U.S. EPA, 1995).

II.C. PM Doses in Children from Increased Ventilation Rates

While the fraction deposited on a mass basis is not generally very different between adults and children, differences in levels of activity between adults and children play a large role in age-related differences in their respective doses of ambient particles. Children generally have higher activity levels during the day (as noted above), yielding higher daily minute ventilation,

especially when viewed on a per body weight basis. The typical total volume (m3) breathed in 24 hours for children (0-5 years) is 11.6; children (6-13 years) is 18.2; and for children (14-18 years) is 25.5. The above childhood ventilation rates compare with an average 19.4 m3 breathed in 24 hours for male worker (18-44 years of age). Thus, even without adjusting for body weight or lung surface area, teenagers breathe a greater volume of air than adults, due to their more active lifestyles, which increases the PM pollution dose they receive. Combining the deposition information in Figure 2 with these ventilation rates, it is seen in Figure 3 that children generally receive a greater inhaled dose of particle mass per given ambient PM mass concentration, especially in children aged 14-18.

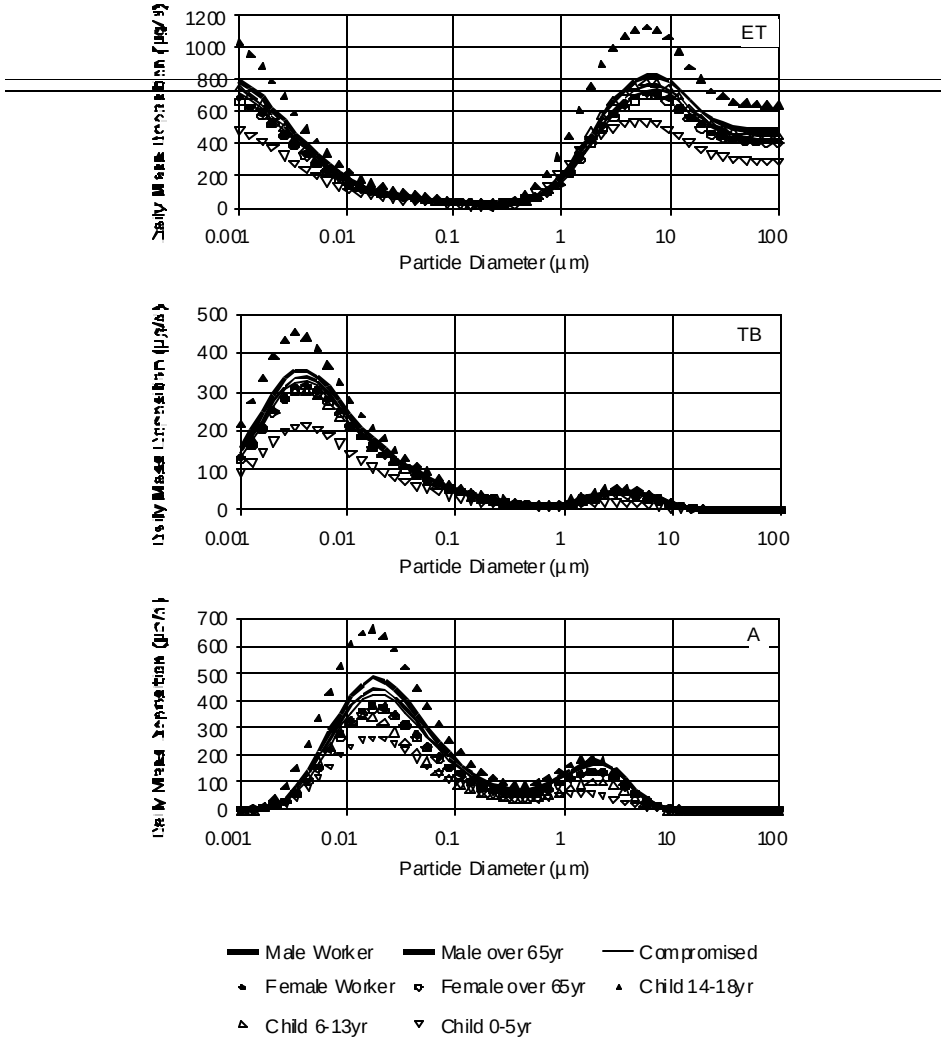

Figure 3. Daily PM deposition rates (ug/day) for 24 hour exposure at 50 ug/m^3 in each respiratory tract region as predicted by the International Commission on Radiological Protection (ICRP66).(U.S. EPA, 1996).

II.D. Doses of Ultrafines among Children 14-18 Years of Age

It is important to note, when evaluating the enhanced mass deposition in the ultrafine fraction for children 14-18 years of age, that the number of particle "hits" may be of paramount importance to health, rather than the PM_{10} mass. Thus, the enhanced alveolar deposition mass shown in Figure 3 in the ultrafine range represents a significant increase in the total number concentration dose experienced by children. The enormous numbers and huge surface area of the ultrafine particles demonstrate the importance of considering the size of the particle in assessing response. Ultrafine particles with a diameter of 20 nm when inhaled at the same mass concentration have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5 um diameter particle, and particle surface area is also greatly increased, as shown in Table 2.

Table 2. Numbers and Surface Areas of Monodisperse Particles of Unit Density of Different Sizes at a Mass Concentration of 10 $\mu g/m^3$

Particle Diameter (μm)	Particle Number (per cm^3 Air)	Particle Surface Area (μm^2 per cm^3 Air)
0.02	2,400,000	3,016
0.1	19,100	600
0.5	153	120
1.0	19	60
2.5	1.2	24

Source: Oberdorster et al. (1995).

If the number concentration exposure in the alveolar part of the lung is of great health significance, as has been hypothesized by Seaton et al. (1995), then the greater ultrafine exposure in children 14-18 could take on greater importance than the disparities indicated by adult versus childhood mass concentration exposures and doses. Indeed, many studies summarized in the U.S. Environmental Protection Agency's PM Criteria Document (1995) suggest that the surface of particles, or substances that are on or are released from the surface (e.g., acids and/or transition metals), interact with the biological system and that surface-associated free radicals or free radical-generating systems may be responsible for toxicity. Thus, if ultrafine particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the relatively large surface area for a given mass of ultrafine particles would mean higher concentrations of transition metals being available to cause oxidative stress to cells in the lungs of children vs. adults who breathe these aerosols.

II.E. Biological Factors that Increase PM Susceptibility in Children

In addition to differences in the ambient concentrations that children are exposed to relative to adults, the implications of those exposures are different due to biological differences between adults and children. In this section, these differences and their implications are discussed.

1. Enhanced PM Doses in Children per Body Weight and Lung Surface Area

In addition to the fact that children can get higher absolute PM doses due to their greater activities and higher PM personal clouds, children also have smaller lungs and much lower body weights, both of which increase the toxicity of a given PM dose. For example, a newborn typically weighs 3 kg, a young child 10 kg, an older child 33 kg, and an adult 70 kg (Snodgrass, 1992). Thus, PM doses, when viewed on a per kg body weight basis, are much higher for children than adults. This is graphically displayed in Figure 4, which indicates that the amount of air inhaled per kg body weight increases dramatically as age decreases below adult levels, with the inhalation rate (in m^3/kg/day) of a 10-year old being roughly twice that of a 30-year old person, and this estimate does not even consider the higher personal exposure concentrations that a child is usually exposed to as a result of his or her high activity levels. Thus, for a given exposure concentration, young children get roughly 3 times higher air pollution doses than do adults, when viewed on a per unit body weight basis.

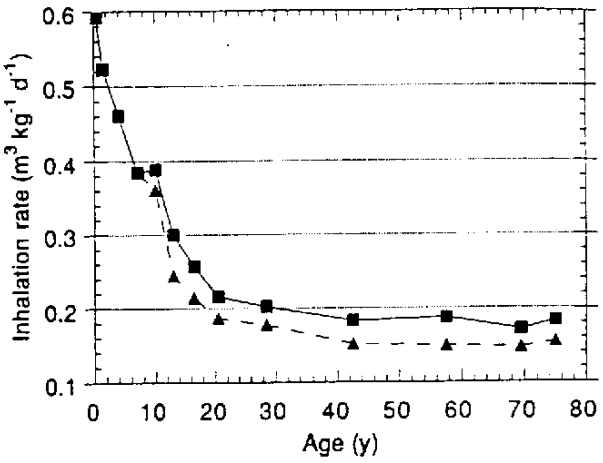

FIGURE 4. Inhalation rates on a per body-weight basis for males (ν) and females (σ) by age. (Layton, 1993).

Child-adult dosage disparities are even greater when viewed on a per lung area basis, which may be more important than body weight if the number of particle "hits" per unit lung surface is the important health impact metric, which may well be the case for ultrafine particles. A newborn infant has approximately 10 million alveoli vs. some 300 million as an adult. The

alveolar surface area increases from approximately 3 m^2 at birth to about 75 m^2 in adulthood, causing infants' and children's doses per lung surface area to be much higher than in adults, even given the same personal exposures (which is not the case, as they generally have greater PM_{10} personal exposures than adults, as noted above). Thus, PM air pollution doses are significantly higher in children than adults when one considers their higher personal exposures, their greater activity rates, and their smaller body weights and lung surface areas.

2. Diminished and Developing Defense Systems in Infants

As discussed by Plopper and Fanucchi (2000), the limited experimental and epidemiologic studies currently available identify the early post neonatal period of lung development as a time of high susceptibility for lung damage created by exposure to environmental toxicants. For example, due to the relatively diminished defenses of their developing immune systems, infants are disproportionately susceptible to infections and other diseases. Indeed, in 1998 in the U.S., the rate (per 1000) of Meningococcal disease by age group was 11.47 for <1 year versus: 2.75 for 1-4 years; 0.90 for 5-14 years; 1.27 for 15-24 years, 0.41 for 25-39 years; 0.49 for 40-64 years; and, 1.13 for >=65 years (CDC, 1999). Recent research indicates that there is a relationship between respiratory infections and air pollution effects in children (Sarafino et al., 1998). Thus, the higher rate of infectious diseases among infants is an indicator of diminished defenses against health insults, and is likely to cause them to have diminished reserves, and therefore to be more greatly affected by exposures to air pollution.

In addition to their insufficiently developed immune systems, infants are growing rapidly, and limited recent evidence supports the hypothesis that environmental pollution can significantly alter development of the respiratory system at that period of life. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi, 2000; Fanucchi and Plopper, 1997). In addition, acute injury to the lung during early postnatal development causes a failure of normal repair processes, including down-regulation of cellular proliferation at sites of injury in animals. (Smiley-Jewel, et al., 2000, Fanucchi et al., 2000). Thus, it may be that both infants' diminished defenses and pollution-induced impairment of repair mechanisms can therefore coincide during infancy, making the neonatal and post-neonatal period one of especially elevated susceptibility to damage by environmental toxicants like PM.

III. KEY STUDIES OF PM AND SULFATE HEALTH EFFECTS

As discussed by Bates (1995), air pollution has been documented for many decades to be associated with a wide variety of health impacts in humans, and especially among the elderly and children. Indeed, as shown in the table below, infants less than one year of age (0-1 months Neonatal, 1-12 months Post-neonatal) experienced larger increases in mortality than older children or young adults during the notorious London Fog air pollution episode of 1952, and infants are indicated to be an especially susceptible subgroup of children. Among adults, recent research indicates that those with prior or coincident respiratory infections are among those especially affected by air pollution (Zanobetti et al, 2000), which may also be a factor placing infants at higher risk of being affected by air pollution, given their high rates of infectious diseases.

Table 3. Deaths Registered in London Administrative County Classified by Age (Bates, 1995)

	< 1 Month of Age	1-12 Mo. Old	1-14 Years of Age	15-44 Years of Age	45-64 Years of Age	65-74 Years of Age	75+ Years of Age
Week Before the Episode	16	12	10	61	237	254	335
Week After the Episode	28	26	13	99	652	717	949
Before/After Episode Ratio	1.75	2.17	1.3	1.62	2.75	2.82	2.83

More recent epidemiological evidence indicates that lower present-day ambient PM air pollution exposure is also associated with adverse health effects in children in general, and, as will be discussed in detail below, these effects can include:

From short-term PM exposures to children:

- reduced pulmonary function;
- increased respiratory symptoms in asthmatics (e.g., asthma attacks) and non-asthmatics;
- increased incidence of respiratory doctor's visits;
- increased incidence of emergency department (ED) visits and hospital admissions (HA's);
- increased mortality, and;
- especially increased infant morbidity and mortality;

From long-term chronic PM exposures to children:

- Reduced lung function;
- increased respiratory symptoms; and,

- Increased infant mortality, intrauterine growth reduction, or pre-term delivery.

The PM indices most commonly evaluated in epidemiological and toxicological studies are those that have been most routinely measured: PM_{10}, total suspended particulate matter (TSP), and Black Smoke (BS, an index of primary carbonaceous particle mass collected primarily in Britain and Europe). However, significant effects are also reported for less often measured $PM_{2.5}$, sulfates ($SO_4^{=}$), and acidic aerosols (H^+).

This section seeks to summarize the most pertinent available evidence for acute and chronic health impacts of particulate matter and sulfates (including relevant toxicology, controlled exposures, and epidemiological studies, as available). These discussions emphasize studies involving children and adolescents, but rely on studies among adults when children's studies are not available. This section will also include, to the extent that information is available, a discussion of any special biological reasons for, or scientific evidence of, elevated susceptibility of infants and children to particulate matter and sulfates, in comparison to the general population.

III.A. Lung Function and/or Respiratory Symptom Effects from Acute PM Exposures

While not as adverse as more severe outcomes, such as medical visits or hospital admissions, symptom and lung function impacts do provide supportive evidence of consistent effects across outcomes, and can become medically important in health impaired individuals (e.g., children with asthma). A variety of PM and or sulfate symptom effects have been found in children, particularly in U.S. studies conducted in California. Cough, phlegm, and lower respiratory infections (LRI) are sometimes found to be associated with air pollution in these studies. Delfino and colleagues' (1998) California study reported stronger symptom effects for 1-h and 8-h PM_{10} exposures, rather than 24-hr average PM_{10}, is noteworthy. This may indicate the need for a PM standard applicable to more acute exposure peaks of only a few hours.

Many asthmatics self-medicate with bronchodilators, which may also be a useful indicator of respiratory distress in these subjects. In the case of the Thurston et al. (1997) study of children with asthma at a summer camp, the medications were prescribed in cases where an asthma exacerbation was verified by a resident physician, indicating this to be a metric of severe air pollution effects associated with acidic sulfates (and ozone) in this case. A number of investigators have found statistically significant peak expiratory flow reduction (PEFR)

associated with PM_{10} and other PM indices, and some have reported significant reduction in FEV_1 and FVC. For example, Figure 5 shows the relationship found between sulfates and PEFR, lower respiratory chest symptoms, and medication use in children with asthma in the Thurston et al summer camp study.

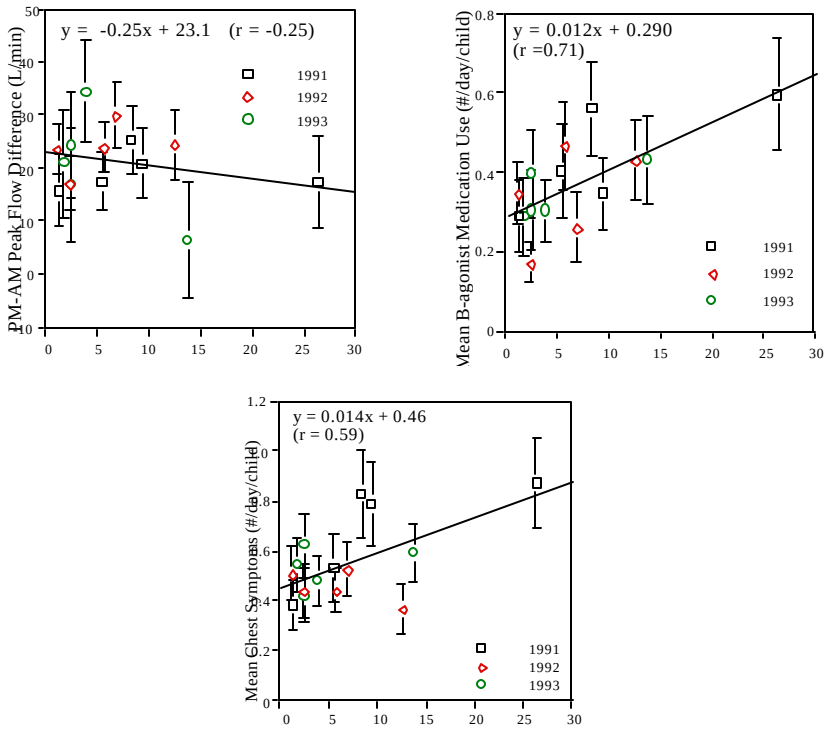

Figure 5. Lung Function, Symptom, and Inhaler Medication Use Association with Sulfate Concentration in children (ages 8-12) with asthma at a summer camp (Thurston et al., 1997)

Thus, as indicated by the studies summarized in Table 4, there is an overall indication that respiratory symptoms in children are exacerbated by exposure to airborne particles and sulfates. These effects have greater health implications in children with asthma, and can and do lead to an increased incidence of asthma attacks. Since the prevalence of asthma is much higher among children than among adults (CDC, 1996a,b), these enhanced acute effects of air pollution on those with asthma put more children at higher risk of PM health effects than adults.

III.B. Lung Function and/or Respiratory Symptoms from Long-Term PM Exposures

For decades, there has been accumulating evidence suggesting that higher long-term ambient particulate matter exposures are associated with higher rates of chronic respiratory disease. Much of this evidence has been based on cross-sectional analyses, comparing disease or symptom prevalence rates in different communities with different average pollution levels (e.g.,

Ferris et al., 1973; 1976; Hodgkin et al., 1984; Mullahy and Portney, 1990). This type of study is able to indicate associations, but they are often criticized because these analyses cannot be controlled for confounding factors on an individual level, and are more likely to be subject to ecological confounding than prospective cohort studies. Also, chronic symptoms presumably occur as a result of long-term exposures, but cross-sectional analyses are not very informative as to whether, for example, it is the five-year average, the twenty-year average, or the number of times a given level is exceeded that is the relevant health effects exposure measure.

TABLE 4. Recent U.S. Panel Studies Of Pulmonary Function Tests or Acute Respiratory Symptoms Associated with PM Exposure in North American Children

Study	Health Endpoints	Ages (yrs.)	PM Effects	Pollutants Considered	Remarks (N)
Ostro et al. (1995) Los Angeles, CA	Asthma symptoms for at least six weeks	7-12	Shortness of breath risk, 9% per 10 ug/m^3 PM_{10}	PM_{10}, TSP, SO_4, NO_3, O_3, SO_2, NO_2	African-American (N = 83)
Delfino et al. (1998) Alpine, CA	Bothersome asthma symptoms	9-17	Symptoms signif. 1-h, 8-h PM_{10}, 24-h less signif.	PM_{10}, O_3 (others low)	Panel of asthmatics (N = 25)
Delfino et al. (1997) Alpine CA	Symptom score, bronchodilator use		PM_{10} signif. dilator use	PM_{10}, O_3	Asthmatics (N = 13)
Delfino et al. (1996), San Diego, CA	Symptom scores, bronchodilator use		Signif. O_3 personal monitor, N.S. SAM O_3, $PM_{2.5}$	$PM_{2.5}$, O_3	Asthmatics (N = 12)
Hoek et al. (1998) re-analyses of 4 other studies in the U.S. and the Netherlands	PEF, large changes related to symptoms		Signif. PEFR, Cough PEFR N.S. PEFR N.S. PEFR N.S.	PM_{10}	Utah Valley Bennekom Uniontown St. College
Linn et al. (1996) southern CA	Pulmonary function		Morning FVC signif. PM5?, NO_2	PM5?, NO_2	School children (N = 269)
Thurston et al. (1997) Connecticut summer camp	lung function, symptoms, dilator use	8-12	SO_4, O_3 assoc. with symptoms, PEFR, dilator use	PM_{10}, SO_4, H+, O_3,	Asthmatic children (n=55)

Key: PEF = peak expiratory flow; PEFR = reduction in PEF; N.S.= not statistically significant (two-tailed, P > 0.05).

Source: Adapted from US EPA (1998)

More recently published articles have followed cohorts, answering the major criticisms of past studies by allowing confounder controls at the individual level. Abbey and colleagues (1991; 1993; 1995a,b) have reported results of a 10-year cohort study conducted at Loma Linda University in California with a large sample of nonsmoking adults. This follow-up allowed for measures of exposure over the 10-year period and for obtaining information on changes in chronic respiratory disease incidence over time. Abbey et al. (1995a) extends those earlier studies by analyzing associations between these chronic respiratory disease outcomes and both fine particles and sulfates. Logistic models were fitted using the mean concentration of these

two pollutants, along with PM_{10}, ozone, and other pollutants. Fine particles were estimated from empirical estimates related to airport visibility. Regarding sulfates, a statistically significant association was observed with airway obstructive disease (AOD). Abbey and colleagues found no association with either SO_2 or NO_x, but sulfate exposure was associated with changes in the severity of AOD and chronic bronchitis over the ten-year study period. Thus, new cases of disease were able to be analyzed in relation to pollution exposure for a matching time period in these studies, providing a more definitive concentration-response function for chronic respiratory disease, while confirming past "ecological" study results.

Children are likely to be at greater risk from long-term exposures because their bodies are growing, and their developmental processes, especially in the lung, may well be interfered with by air pollution exposures. Table 5 shows a number of recent studies involving school-age children indicating adverse respiratory effects from longer-term PM exposures. PM_{10} is not always significantly associated with adverse health effects in these studies, although other PM indicators sometimes are (e.g., $SO_4^{=}$, H^{+}). The mechanisms by which elevated PM exposure over long periods of time may be associated with increased risk of respiratory symptoms or decreased pulmonary function in children are not now understood, but may be analogous to the cumulative effects of smoking or environmental tobacco smoke (ETS) on the human respiratory system.

TABLE 5. Recent PM Studies Of Pulmonary Function Tests Or Respiratory Symptoms Associated With Long-Term PM Exposure In North American School-Age Children

Study	Endpoint	Ages (years)	Significant PM Associations	Pollutants Considered	Remarks (N)
Dockery et al. (1996) 24 U.S. & Can.. Communities	Various	8-12	SO_4 signif. bronchitis; PM_{10} N.S. any endpoint	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Raizenne et al. (1996) 24 U.S., Canadian Communities	Pulmonary function	8-12	Strong signif. H+, Signif. PM_{10}	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Peters et al. (1999a,b) 12 So. CA communities	Asthma, bronchitis, cough, wheeze, lung function	9-12	PM_{10} signif. FVC, FEF25-75% N.S. FEV_1, symptoms, PEFR,		(N =150 each, in grades 4, 7)

Source: Adapted from US EPA (1998)

III.C. Incidence of Medical Visits and Hospital Admissions from Acute PM Exposures

Numerous studies have related acute PM exposure with an increased incidence of hospital admissions (e.g., see Figure 6), but only a limited number have specifically studied the subgroup that are children. Burnett et al (1994) examined the differences in air pollution-

hospital admissions associations as a function of age in the province of Ontario. As shown in Table 6, this analysis indicated that the largest percentage increase in admissions was found among infants (neonatal and post-neonatal, one year or less in age), just as was the case for the mortality effects during the London fog of 1952 (see Table 3).

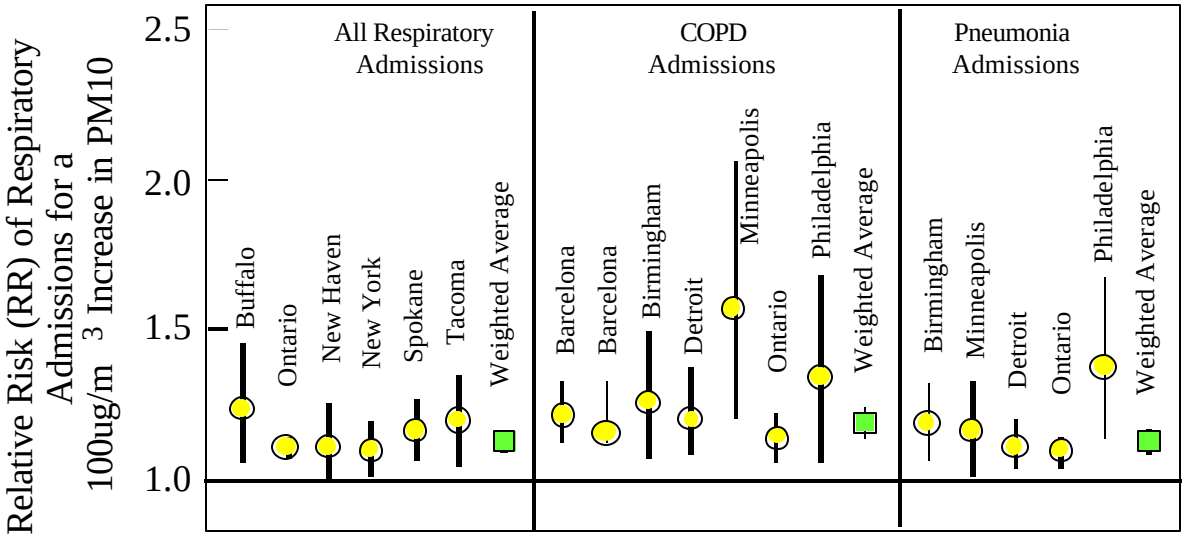

Figure 6. Summary of Respiratory Hospital Admissions-PM_{10} Relative Risk Estimates from Air Pollution Studies Around the World (Schwartz, 1997)

Table 6. Percent Increase in Respiratory Hospital Admissions Associated with Sulfate (5.3 ug/m^3) and Ozone (50 ppb) Air Pollution in Ontario, Canada, by Age (Burnett et al, 1994)

	< 1 Year of Age	2-34 Years of Age	35-64 Years of Age	75+ Years of Age
Asthma Admissions	13.0	5.5	9.8	7.0
Total Respiratory Admissions	14.8	5.5	7.2	4.3

More recent hospital admissions studies listed in Table 7 also indicate positive and often statistically significant associations between PM exposures and medical visits or hospital admissions by children. However, some of these PM-health effect associations listed in Table 7 became statistically non-significant when gaseous co-pollutants were included in the model, including O_3, SO_2, NO_2, CO. This may be due to a statistical artifact of pollutant inter-correlations over time causing enlarged coefficient standard errors, or may suggest that the co-pollutant mixture can collectively play a role in the effects of PM on children (e.g., through gas-particle interactions).

TABLE 7. Recent Key PM Studies Of Associations Between Medical Visits Or Hospital Admissions and Short-Term PM Exposure In Children

Study	Endpoint	Ages (yrs.)	PM Effects	Pollutants	Remarks (N)
Delfino et al. (1997) Montreal PQ	Emergency Dept. Visits (EDV), 1992-1993	0-1	H+ signif. only 1993	PM_{10}, $PM_{2.5}$, SO_4, H+, O_3	
Medina et al. (1997) Paris, France	Doctor's house calls	0-14	Asthma signif. BS.	PM_{13}, BS, SO_2, NO_2, O_3	Similar RR for PM13, SO_2, NO_2
Sunyer et al. (1997) Barcelona Helsinki London, Paris	emergency hospital admissions (HA's) for asthma	0-14	BS positive, N.S. NO_2 and SO_2 signif.	BS, NO_2, SO_2	
Anderson, et al. (1998) London, UK	HA's for asthma	0-14	BS positive, Signif.	BS, O_3, SO_2, NO_2	O_3, SO_2, NO_2, BS all pos. assoc.
Garty et al. (1998) Israel	EDV for asthma	1-18	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2	N = 1076
Morgan et al, 1998 Sydney, AU	Asthma, COPD, and Cardiac HA's	0-14	PM (nephelometry) NS, NO_2 signif.	PM (nephelometry), O_3, and NO_2	
Rosas et al. (1998) Mexico City	emergency HA's for asthma	0-15	PM_{10} N.S.	PM_{10}, TSP, O_3, SO_2, NO_2	grass, fungal spores signif.
Atkinson et al. (1999) London UK	EDV for respiratory complaints	0-14	PM_{10} signif. total resp., asthma	PM_{10}, BS, O_3, SO_2, NO_2, CO	N.S. in 2-poll. models w. SO_2, NO_2
Atkinson et al. (1999) London UK	Hospital admissions for respiratory complaints	0-14	PM_{10} signif. total resp., asthma	PM_{10}, BS, O_3, SO_2, NO_2, CO	N.S. in 2-poll. models w. SO_2, NO_2
Norris et al. (1999) Seattle WA	EDV for asthma	0-17	PM_{10} signif. all hosp., lt.-scatter each	PM_{10}, light scatter, CO, SO_2, NO_2	PM_1 index from light scattering
Lin et al. (1999) Sao Paulo, Brazil	Respiratory emergency visits	0-12	PM_{10} signif. w. and w/o co-pollutants	PM_{10}, O_3, SO_2, NO_2, CO	LRI, URI, wheezing w. co-pollutants
Braga et al. (1999) Säo Paulo, Brazil	Hospital admissions	0-12	PM_{10} signif., not w. O_3, CO	PM_{10}, SO_2, NO_2, CO	
Ostro et al. (1999) Santiago, Chile	Medical visit for LRI, URI	<2 2-15	LRI 4-12% LRI 3-9%	PM_{10}, O_3	
Hajat et al. (1999) London U.K.	GP visits for asthma, LRI	0-14	PM_{10} N.S., BS signif. LRI	PM_{10}, BS, O_3, SO_2, NO_2, CO	
Wong, et al (1999) Hong Kong, CH	Respiratory HA's	0-4	PM_{10} NO_2, and O_3 signif., SO_2 not signif.	PM_{10}, NO_2, SO_2, O_3	
Gouveia et al (2000) Sao Paulo, BR	Respiratory, Pneumonia, and asthma HA's	<1 <5	Only PM signif., with larger RR than for <5 (pneumonia) All poll RR's>1, but NS. for asthma. Only SO_2 signif for Pneum., and only O_3 signif. for all resp.	PM_{10}, NO_2, SO_2, O_3	

Source: Adapted from US EPA (1998)

Looking in more detail at the results from each study in Table 7, as provided in the Appendix A Tables, reveals that the PM RR's for all children (e.g., 0-14 yrs.) are not usually noticeably larger than those for adults, but such comparisons of RR's must adjust for differences in the baseline risks for each group. For example, if hospital admissions per 100,000 per day for young children are double the rate for adults, then they will have a pollution relative risk (RR) per ug/m^3 that is half that of the adults given the exact same impact in

admissions/100,000/ug/m^3/day. Thus, it is important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is usually not available (especially the population catchment for each age group in each study). One of the only signals that comes out clearly when comparing children with adults in the Appendix A Tables is for the group <1 yr. of age, which (despite higher baseline rates) usually has RR's larger than for other children or adults, as previously found in the Burnett (1994) study.

Two recent studies have found that air pollution-admissions associations are also stronger for the poor, which has special implications for children. Nauenberg et al. (1999) analyzed the effect of insurance status on the association between asthma-related hospital admissions and exposure to atmospheric particulate matter (PM_{10}) and ozone (O_3) using hospital discharge and air quality data for 1991-1994 for central Los Angeles. They used regression techniques with weighted moving averages (simulating distributed lag structures) to measure the effects of exposure on overall hospital admissions, admissions of uninsured patients, admissions for which MediCal (California Medicaid) was the primary payer, and admissions for which the primary payer was another government or private health insurance program. No associations were found between asthma admissions and O_3 exposure in LA. An estimated increase from 1991 to 1994 of 50 micrograms per cubic meter in PM_{10} concentrations averaged over eight days was, however, associated with an increase of 21.0% in the number of asthma admissions. An even stronger increase--27.4%--was noted among MediCal asthma admissions. The authors conclude that low family income, as indicated by MediCal coverage, is a useful predictor of strength of asthma associations with air pollution. Similarly, Gwynn and Thurston (2000) have recently found that air pollution effects are worse in the poor and working poor than in other groups, and that these differences account for apparent racial differences in air pollution effects in New York City. These studies' results both indicate that children are especially at risk from air pollution, as they more often live in poverty than any other age group (e.g., in 1989, 27.3% of children in LA lived in poverty, as compared to 18.9% overall, and 10.5% for those 65+ years of age) (U.S. Census, 1994).

III.D. Infant and Child Mortality Associated with Acute PM Exposures

Table 8 shows the results of recent studies in which excess mortality was associated with PM. Significant mortality was reported in three of the four studies, using $PM_{2.5}$ exposure for infants in Mexico City (Loomis et al., 1999), TSP exposure for school- age children (but not

younger children) in Delhi (Cropper et al., 1997), and PM_{10} exposure for a composite group of children 0-5 years in Bangkok (Ostro et al., 1998). Pereira et al. (1998) did not find excess stillbirths associated with PM_{10} in Sao Paulo. These studies are highly diverse in terms of age group, location, and environment. As with adult mortality, we do not now know the exact biological mechanisms that specifically account for excess child mortality from short exposures to PM at levels found in these Latin American and Asian countries. However, the available studies suggest that short-term PM exposure in general may cause deaths of some children in urban environments. The mortality findings are consistent with findings noted above of less serious health effects from short-term PM exposure, including lung function decreases, respiratory symptoms, asthma attacks and medical visits that may affect substantial numbers of children.

Table 8. Neonatal, Infant, And Child Mortality Attributable To Short-Term PM Exposure

Study	Mortality	Ages	PM Effects	Pollutants	Remarks (N)
Loomis et al. (1999) Mexico City	Total	0-11 mo.	$PM_{2.5}$ signif. w and w/o co-pollutant	$PM_{2.5}$, O_3, NO_2	
Pereira et al. (1998) São Paulo, Brazil	Intrauterine	0 d	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2, CO	
Cropper et al. (1997) Delhi, India	Total, cardiovascular, respiratory	0-4 yr. 5-14 yr.	TSP N.S. for total mort. TSP signif. for total mort	TSP, SO_2, NO_x	Similar RR in both age groups
Ostro et al. (1999) Bangkok, Thailand	Total, cardiovascular, respiratory	0-5 yr.	PM_{10} signif. all	PM_{10}, $PM_{2.5}$	

Source: Adapted from US EPA (1998)

III.E. Increased Infant and Child Mortality Associated with Long-Term PM Exposures

A number of studies suggest that the very young represent an especially susceptible sub-population, although the precise magnitude of the effects of specific levels of air pollution can be expected to vary with other underlying conditions. Lave and Seskin (1977) found mortality among those 0-14 years of age to be significantly associated with TSP. More recently, Bobak and Leon (1992) studied neonatal (ages less than one month) and post-neonatal mortality (ages 1-12 months) in the Czech Republic, finding significant and robust associations between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in simultaneous regressions. Woodruff et al. (1997) used cross-sectional

methods to follow-up on the reported post-neonatal mortality association with outdoor PM_{10} pollution in a U.S. population. This study involved an analysis of a cohort consisting of approximately 4 million infants born between 1989 and 1991 in 86 U.S. metropolitan statistical areas (MSA's). After adjustment for other covariates, the odds ratio (OR) and 95% confidence intervals for total post-neonatal mortality for the high exposure versus the low exposure group was 1.10 (CI=1.04-1.16). In normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI=1.05-1.85) and also with sudden infant death syndrome (OR = 1.26, CI=1.14-1.39). Among low birth weight babies, which are lower in counts (and therefore with greater uncertainty and power) high PM_{10} exposure was associated, but not significantly, with mortality from respiratory causes (OR = 1.18, CI=0.86-1.61).

The Woodruff et al. (1997) study was recently corroborated by a more elegant follow-up study by Bobak and Leon (1999), who conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. They used conditional logistic regression to estimate the effects of suspended particles, sulfur dioxide, and nitrogen oxides on risk of death in the neonatal and post-neonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of all pollutants were strongest in the post-neonatal period and were specific for respiratory causes. Only particulate matter showed a consistent association when all pollutants were entered in one model. Thus, it appears that PM is the air pollutant metric most strongly associated with excess post-neonatal deaths.

Collectively, all the recent studies of children less than one year old presented in Table 9 indicate severe adverse consequences to the mother, fetus, and infant from prolonged PM exposure during and shortly after pregnancy. There appears to be a possible relationship between preterm birth (< 37 weeks gestational age) or low birth weight (< 2,500 g) and PM exposure in several locations. A significant relationship with PM_{10} and $PM_{2.5}$ was found in Teplice, Czech Republic (Dejmek et al., 1999), but not with PM_{10} in Los Angeles (Ritz and Yu, 1999). In the case of Ritz and Yu, CO was significant, which might well be serving as an index of traffic-related pollution effects, and therefore possibly related to diesel particulate matter (DPM), but this is not evaluated. Bobak and Leon (1999) did not find a relationship of low birth weight to TSP. There was a significant risk of low birth weight and pre-term delivery in Beijing (Xu et al., 1995; Wang et al., 1997) associated with TSP, but SO_2 was the only co-pollutant

considered. However, low birth weight is known to be an important risk factor for infant mortality, so that the findings of excess mortality in U.S. and Czech infants (Woodruff et al., 1997; Bobak and Leon, 1999) are consistent with many of the other findings on intrauterine growth reduction (IUGR), which is supportive of a causal relationship between PM exposure and adverse health effects in this age group.

Several methodological differences across studies make generalized conclusions more difficult to make. Dejmek et al. (1999) characterize IUGR as low-weight-for-gestational-age, whereas others use a fixed weight for full-term infants (37 to 44 weeks) without adjusting for gestational age. Dejmek et al. (1999) also find the average PM during the first month of pregnancy as the index of fetal exposure, whereas Xu et al. (1995), Wang et al. (1997), and Ritz and Yu (1999) use final trimester averages. Despite these methodological differences, there appears to be an identifiable PM risk to the fetus and infant.

A very recent study of infant mortality in U.S. counties indicates that these effects can occur in the U.S., as well (Chay and Greenstone, 1999). This study uses sharp, differential air quality changes across sites attributable to geographic variation in the effects of the 1981-82 recession to estimate the relationship between infant mortality and particulate matter air pollution. It is shown that, in the narrow period of 1980-82, there was substantial variation across counties in changes in particulate (TSP) pollution, and that these differential pollution reductions appear to be independent of changes in a multitude of other socio-economic and health care factors that may be related to infant mortality. The authors find that a 1 ug/m^3 reduction in TSP resulted in about 4-8 fewer infant deaths per 100,000 live births at the county level of the roughly 1,300 U.S. infant deaths in the first year of life per 100,000 live births (a 0.35-0.45 elasticity). The estimates are remarkably stable across a variety of specifications. The estimated effects are driven almost entirely by fewer deaths occurring within one month and one day of birth (i.e., neonatal), suggesting that fetal exposure to pollution may have adverse health consequences. The estimated effects of the pollution reductions on infant birth weight in this study provide evidence consistent with the infant mortality effects found, suggesting a causal relationship between PM exposure and infant mortality, especially in the first month of life.

Table 9. Adverse Infant Health Effects Associated With Long-Term PM Exposure

Study	Effects	Ages	PM Effects	Pollutants	Remarks (N)
Bobak and Leon (1992) Czech. Repub.	Total infant mortality, respir. mort.	0+ d neonatal post-neonatal post, respir.	TSP-10 N.S. TSP signif. TSP signif.	TSP-10, SO_2, NO_x	Ecologic study; TSP indexed as 90th percentile
Bobak and Leon (1999) Czech. Rep.	Low birth wt. Stillbirth	0 d	TSP N.S.	TSP, SO_2, NO_x	
Chay and Greenstone (1999) California Counties	Infant mortality	0-1 yr.	TSP Signif.	TSP	1 ug/m^3 reduction associated with 4-8 fewer deaths per 100k live births
Dejmek et al. (1999) Teplice, Czech. Rep.	Intrauterine growth reduction	0 d	First month $PM_{2.5}$ > 37, PM_{10} > 40 signif.	PM_{10}, $PM_{2.5}$, SO_2, NO_x, PAH	30-d avg. PM per month of pregnancy
Ritz and Yu (1999) Los Angeles, CA	Low birth weight (adj. Gest age)	0 d	Last trimester PM_{10} N.S.	PM_{10}, O_3, NO_2, CO	CO signif., may be index of traffic air poll., e.g. DPM
Wang et al. (1997) Beijing, PRC	Low birth weight	0 d.	TSP signif. increases risk of LBW	TSP, SO_2 in third trimester	SO_2 also signif. Small reduc. mn.wt.
Woodruff et al. (1997)	Total infant mortality, SIDS, resp.	1-11 mo.	PM_{10} signif. total, SIDS, respir. NBW	PM_{10}	PM_{10} avg. over 2 mos.
Xu et al. (1995) Beijing, PRC	Preterm gestational age	0 d	TSP signif. lag 5-10 days	TSP, SO_2	SO_2 also signif.

Source: Adapted from US EPA (1998)

III.F. Evidence for a Role of Sulfates in PM Health Effects

The characteristics of particles responsible for the adverse health effect associations of PM are not yet known. However, lung injury has been postulated to be mediated by ultrafine particles, biological agents (e.g., endotoxin), acid aerosols, organic fraction of PM and oxidant generation catalyzed by transition metals associated with particles. Of these, the role of acidic combustion aerosols and their possible mechanisms for effects are among the best documented.

While significant associations are sometimes reported between total suspended particulate (TSP) and health effects in large populations, the degree of association in studies comparing various PM indices (e.g., Ozkaynak and Thurston, 1987; Dockery et al., 1993; Thurston et al., 1994) is as follows:

$$TSP < PM_{10} < PM_{2.5} < SO_4^{=}$$

Each metric is essentially a subset of the one to its left, implying that $SO_4^{=}$, or something in the mixture closely associated with it, is a likely causal factor in the effects reported.

The sulfate ion itself is an unlikely causal factor if it is in a neutralized state. It is already present in body fluids at relatively high concentrations, and controlled inhalation studies in humans and laboratory animals of pH neutral or nearly neutral sulfate salts, such as ammonium sulfate [$(NH_4)_2SO_4$], even at relatively high concentrations, produce none of the effects reported from the epidemiologic studies (Utell et al., 1983; Lippmann et al., 1987; Schlesinger, 1989; Schlesinger et al., 1990). What these controlled exposure studies do show is that sulfate aerosols containing strong acids, such as sulfuric acid (H_2SO_4) and, to a lesser extent, ammonium bisulfate (NH_4HSO_4), do produce functional and structural changes in healthy subjects consistent with those observed in epidemiological studies, and do so at exposures within the upper bounds of current H^+ ambient levels. Furthermore, it is reasonable to speculate that the effects seen in the epidemiological studies are occurring in hyper-susceptible segments of the population, and that controlled exposure studies in susceptible human and animal cohorts, if they could be ethically performed, might well produce comparable effects at low ambient levels of H^+. A working hypothesis, therefore, is that H^+ is a causal factor for human health effects (e.g., see Lippmann and Thurston, 1996) and that, among the commonly measured PM indices, $SO_4^=$ is the best surrogate metric for H^+.

Historical and present-day evidence suggest that there can be both acute and chronic effects by acidic sulfates on human health. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations (on the order of 400 ug/m^3 as H_2SO_4, or roughly 8,000 nmoles/m^3 H^+) may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and SO_2 (Ministry of Health of Great Britain, 1954). In addition, Thurston et al. (1989) and Ito et al. (1993) both found significant associations between acid aerosols and mortality in London during non-episode pollution levels (30 ug/m^3 as H_2SO_4, or approximately 600 nmoles/m^3 H^+), though these associations could not be separated from those for BS or SO_2.

Attempts to date to associate present-day levels of acidic aerosols in the U.S. with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993, Schwartz et al., 1996, and Gwynn, et al., 2000) have had more mixed results, but there may not have been a sufficiently long series of H^+ measurements to detect H^+ associations in many of these studies. In the Utah

Valley studies (Pope et al. 1991, 1992), PM_{10}-health effects association were found, despite limited H^+ sampling indicating low acid aerosol levels. This is not inconsistent with adverse health effects from H^+, however, when it is considered that PM can contain numerous toxic agents other than H^+. The more recent work of Gwynn et al. (2000) reported significant pollutant-health effect associations in Buffalo, NY--most strongly between $SO_4^=$ and respiratory hospital admissions (as indicated by its t-statistic). Additionally, H^+ and $SO_4^=$ demonstrated the most coherent associations with both respiratory hospital admissions and respiratory mortality. The authors concluded that "acidic sulfate aerosols represent a component of PM air pollution that may contribute to the previously noted adverse effects of PM mass on human health."

Pope et al. (1995) linked ambient air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor on 552,138 adults who resided in these areas when enrolled in a prospective study in 1982. Deaths were ascertained through December 1989. Exposure to $SO_4^=$ and $PM_{2.5}$ pollution was estimated from national databases. The relationships of air pollution to all-cause, lung cancer, and cardiopulmonary mortality were examined using multivariate analysis that controlled for smoking, education, and other risk factors at the individual level. An association between mortality and particulate air pollution was observed. Figure 7 shows the range of values for the adjusted mortality rates in the various communities versus annual average $SO_4^=$ concentrations. The Pope et al. (1995) results thus indicate that the concerns raised about the credibility of the earlier results, due to their inability to control for potentially confounding factors such as smoking and socioeconomic variables on an individual level, can be eased, and these findings are consistent with the prior findings of Ozkaynak and Thurston (1987) and Lave and Seskin (1970, 1977). Adjusted relative risk ratios (and 95% confidence intervals) of all-cause mortality for the most polluted areas compared with the least polluted were $RR(SO_4^=)$ =1.15 (1.09 to 1.22) and $RR(PM_{2.5})$ = 1.17 (1.09 to 1.26). The findings of Dockery et al. (1993) and Pope et al. (1995) in prospective cohort studies also indicate that mean lifespan shortening of long-term exposures to PM is of the order of two years (Brunekreef, 1997). This implies that some individuals in the population have lives shortened by many years, and that there is excess mortality associated with long-term fine particle exposure that is greater than that indicated by an accumulation of acute effect estimates provided by the time-series studies of daily mortality.

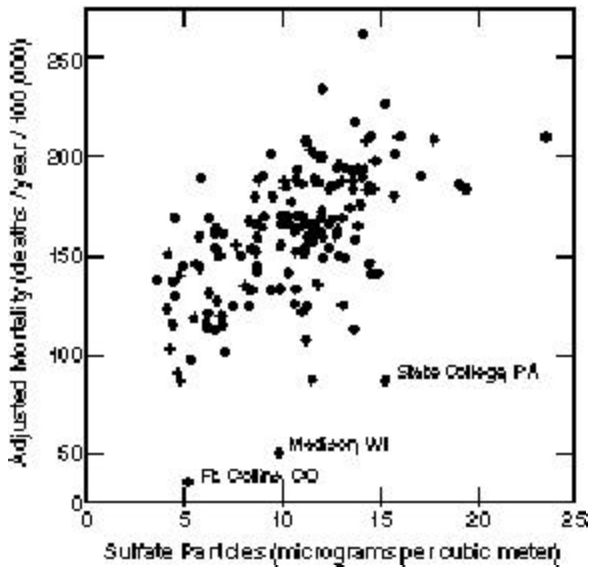

Figure 7. Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against mean sulfate air pollution levels for 1980. Data from metropolitan areas that correspond approximately to areas used in prospective cohort analysis. From: Pope, C.A. et al., Am. J. Respir. Crit. Care Med. 151:669-674 (1995).

Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has also been observed under present-day conditions. Thurston et al. (1992) and Thurston et al. (1994) have noted associations between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding temperature effects. In the latter of these studies, significant independent H^+ effects remained even after simultaneously considering the other major co-pollutant, O_3, in the regression model. While the New York State study considered only ozone as a possible confounder, the Toronto study also considered NO_2 and SO_2, but found them to be non-significant. In the Toronto analysis, the increase in respiratory hospital admissions associated with H^+ was indicated to be roughly six times that for non-acidic PM_{10} (per unit mass). In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes (H^+ > 10 ug/m^3 as H_2SO_4, or 200 nmoles/m^3 H^+). These studies provide evidence that present-day strongly acidic aerosols can represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Burnett et al. (1994) has related the number of emergency or urgent daily respiratory admissions at 168 acute care hospitals in all of Ontario during 1983 to 1988 to estimates of ozone and sulfates in the vicinity of each hospital. The authors reported that SO_2 and NO_2 were

only weakly correlated with SO_4 in these data (r = 0.3), so these pollutants were unlikely to be confounders. Long-wave cycles in the admissions data were removed using a 19-day moving average equivalent high pass filter. A random effects model (wherein hospital effects were assumed to be random) was employed, using the generalized estimating equations (GEE). After adjusting admissions data for seasonal patterns, day of week effects, and individual hospital effects, positive and statistically significant associations were found between hospital admissions and both ozone and sulfates lagged 0 to 3 days. Positive associations were found in all age groups (0 to 1, 2 to 34, 35 to 64, 65+). The bivariate relationship found between adjusted admissions and sulfates in these data are shown in Figure 8. Positive and significant air pollution associations were found for asthma, chronic obstructive pulmonary disease (COPD), and infections, but not for nonrespiratory (control) admissions, nor for respiratory admissions in the winter months (when people are indoors and levels of these pollutants are low). While these analyses employed much more sophisticated statistical methods, the results generally consistent with Bates and Sizto's prior work in this region, though ozone was found to yield a larger effect than sulfates in this study. The authors point out that $PM_{2.5}$ and H^+ are highly intercorrelated with sulfates in the summer months (r > 0.8), and that one of these agents may be responsible for the health effects relationships found with sulfates in this work.

Ostro (1988) also conducted a cross-sectional analysis of the U.S. Inhalable Particle Monitoring Network airborne particulate matter dataset, but analyzed the 1979-1981 annual Health Interview Surveys (HIS) to test if there were morbidity associations coherent with those found for mortality by Ozkaynak and Thurston during this period. Ostro reported a stronger association between several measures of morbidity (work loss days, restricted activity days, etc.) and lagged fine particle estimates than found with prior 2-week average TSP levels in 84 U.S. cities. In this analysis, a Poisson model was employed, due to the large number of days with zero cases in the dependent variables, and the analyses focused on adults aged 18 to 65. Smoking was not considered in the model, since not all metropolitan areas had data, but the correlation between smoking and any of the pollutants was less than 0.03 and non-significant in the one-third of the HIS sample for which smoking data were available. This indicates that, while presumably important to morbidity, smoking is not a confounder to pollutants in such cross-sectional analyses. Ostro concluded that his findings were consistent with the results of

prior cross-sectional analyses reporting an association between mortality and exposures to fine particles and sulfates.

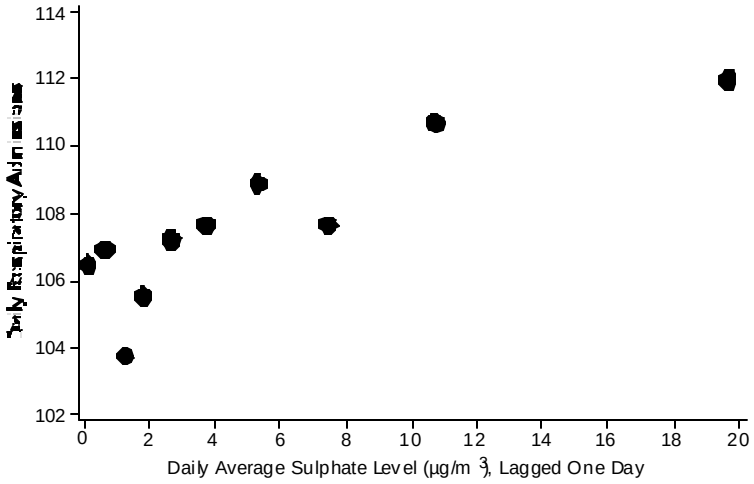

Figure 8. Average number of respiratory admissions among all 168 Ontario hospitals adjusted for other factors, by decile of the daily average sulfate level (ug/m^3), 1 day lag.
Source: Burnett et al., 1994

Taken as a whole, these analyses are suggestive of mortality and morbidity associations with the sulfate fraction of fine particles found in contemporary American urban airsheds. Without nationwide measurements of airborne acidity, however, it is not now possible to evaluate the relative contribution of acid aerosols within these fine particle sulfates to the reported health effects.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic sulfate effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate H^+ associations with lower respiratory symptoms, except at H^+ above 110 moles/m$_3$ (Schwartz et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of H_2SO_4 (Schwartz, et al., 1991b). Some, but not all, recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3 (Studnicka et al., 1995; Neas et al., 1995).

Studies of the effects of chronic H^+ exposures on children's respiratory health and lung function are generally consistent with effects as a result of long-term H^+ exposure. Preliminary

analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested associations between summertime average H^+ and chronic bronchitic and related symptoms (Damokosh et al., 1993). The relative odds of bronchitic symptoms with the highest acid concentration (58 nmoles/m^3 H^+) versus the lowest concentration (16 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1996) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.66, 95% CI: 1.11 to 2.48). It was also found that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1996). Thus, epidemiological evidence indicates that chronic exposures to strongly acidic PM can have effects on measures of respiratory health in children.

One plausible mechanism by which acidic sulfates may act to increase the toxicity of PM is by enhancing the effects of soluble metals and reactive oxygen intermediates. PM, and especially combustion-related aerosols, contain transition metals such as iron, copper, nickel, vanadium, and cobalt that are more readily solublized at lower pH. These metals are capable of catalyzing the one-electron reductions of molecular oxygen necessary to generate reactive oxygen species (ROS) (e.g., via the iron-catalyzed Fenton Reactions. Other than Fe, several vanadium compounds have been shown to increase mRNA levels for selected cytokines in BAL cells and also to induce pulmonary inflammation (Pierce et al., 1996). $NaVO_3$ and $VOSO_4$, highly soluble forms of vanadium, tended to induce pulmonary inflammation and inflammatory cytokine mRNA expression more rapidly and more intensely than the less soluble form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest following exposure to V_2O_5, providing one plausible sulfate PM health effects mechanism.

Many studies investigating the response of animals to particle exposures have used residual oil flyash (ROFA) as a surrogate for ambient particles. ROFA has a high content of water soluble sulfate and metals. As described in the last U.S. PM Criteria Document (U.S. Environmental Protection Agency, 1995), intratracheal instillation of high doses of ROFA suspension generally produced severe inflammation, an indicator of pulmonary injury that

included recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA have been shown to depend on aqueous leachable chemical constituents of the particles. Dreher et al. (1997) have shown that a leachate prepared from ROFA, containing predominantly Fe, Ni, V, Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA suspension, indicating the potency of this sulfate-metals mixture.

IV. PM AND SULFATE INTERACTIONS WITH OTHER POLLUTANTS

This section addresses any studies examining interactions between PM and sulfates and other pollutants (including noncriteria pollutants or bioaerosols).

IV.A. Interaction of PM with Allergens

There is growing scientific evidence that particulate matter from fossil fuel combustion enhances the immune response to allergens, leading to an increase in allergic inflammation and allergic reactivity. Therefore, particulate air pollutants can be an important contributor to the increased morbidity of acute asthma and allergic rhinitis, as well as being a potential trigger of asthma in its own right. Furthermore, recent clinical studies and experimental studies have been able to describe the manner in which diesel particles specifically trigger a biochemical reaction which causes the type of allergic inflammation that asthma medications are aimed at preventing (e.g., see: Nel et al., 1998). Nel and colleagues (1998) have suggested that the rise in the U.S. prevalence rate for allergic rhinitis (5% in the 1950s to about 20% in the 1980s) may be related to increased diesel particulate matter (DPM), in addition to other combustion related PM. Combustion particles may also serve as carrier particles for allergens (Knox et al., 1997). These studies provide biological plausibility for the exacerbation of allergic asthma associated with episodic exposure to PM. Although DPM may make up only a fraction of the mass of urban PM, because of their small size, DPM may represent a significant fraction of the ultrafine particle mode in urban air, especially in cities that rely heavily on diesel-powered vehicles. Thus, while not themselves allergens, diesel and other combustion PM may increase an asthma patient's general responsiveness to any and all allergens and pollens to which they are already allergic, thereby increasing the chance that acute asthma problems will be experienced in a given population of persons with asthma.

Alterations in the response to a specific antigenic challenge have also been observed in animal models at high concentrations of acid sulfate aerosols (above 1,000 ug/m^3) (Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported an enhanced response to non-specific bronchoprovocation agents, such as acetylcholine and histamine, after exposure to inhaled particles. This non-specific airway hyperresponsiveness, a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under controlled conditions (Gearhart and Schlesinger, 1986; Utell et al., 1983). Although its relevance to specific allergic responses in the airways of atopic individuals is unclear, it demonstrates that the airways of asthmatics may become sensitized by acidic sulfates to either specific or non-specific triggers that could result in increases in asthma severity and asthma-related hospital admissions (Peters et al., 1997; Lipsett et al., 1997).

The above noted PM-asthma interactions are of greatest significance to children because the prevalence of asthma children is higher and increasing more rapidly among children than among other age groups. Indeed, the U.S. prevalence rate of asthma in children aged <20 years rose rapidly from approximately 3.5% to 5% during the 1980's, a prevalence that was nearly double adults 20-64 years of age at that time, and higher than all other age groups (U.S. DOH, 1991). Rates for asthma prevalence, hospitalization, and death are especially high among children residing in inner cities, and important risk factors for asthma-related mortality include being poor or black (CDC, 1997a, 1997b). Thus, the above discussed PM-asthma interactions, that suggest that PM air pollution exposure makes people with asthma more reactive to all asthma triggers, mean that children will be at greater risk from PM exposure, as they have the highest prevalence and severity of this worsening disease.

IV.B. Interaction of PM with Gaseous Pollutant Mixtures

Ambient PM usually co-exists in indoor and outdoor air with a number of co-pollutant gases, including ozone, sulfur dioxide, oxides of nitrogen, and carbon monoxide, and this may modify PM toxicity. The presence and nature of any interactions are not well understood at this time, but are likely to depend upon the particle size and the concentration of pollutants in the mixture, exposure duration, and the health endpoint being examined.

One of the primary particle-gas interaction mechanisms documented to-date are chemical interactions between particles and gases that occur on particle surfaces. This forms secondary products on that particle surface that may be more toxicologically active than the primary materials, and that can then be more readily carried to a sensitive sites deeper in the lung. The hypothesis of such chemical interactions has been evaluated in the gas and particle exposure studies of SO_2 and particles by Amdur and colleagues (Amdur and Chen, 1989; Chen et al., 1992). These investigators have demonstrated that synergism occurs as secondary chemical species are produced (e.g., sulfuric acid on the surface of the particles), especially under conditions of elevated relative humidity, such as found in the human lung. Thus, these studies suggest that air quality standards set for individual air pollutants may not be fully protective of human health for exposures to mixed ambient pollutants.

Another hypothesized mechanism of gas-particle interaction may involve pollutant-induced changes in the lung, enhancing the effects of the co-pollutant. For example, Last et al. (1984) indicated that the observed synergism between ozone and acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of ozone by producing a change in the reactivity or residence time of reactants, such as radicals, involved in ozone-induced tissue injury. Kleinman et al. (1999) examined the effects of ozone plus fine H_2SO_4 coated carbon particles (MMAD = 0.26 um) for 1 or 5 days. They found the inflammatory response with the ozone-particle mixture was greater after 5 days (4 hours/day) than after day 1. This contrasted with ozone exposure alone (0.4 ppm) which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure. Thus, acids and ozone together appear to be of greater impact than either alone.

Two studies have examined interaction between carbon particles and gaseous co-pollutants. Jakab et al. (1996) challenged mice with a single 4-hour exposure to a high concentration of carbon, 10 mg/m^3, in the presence of SO_2 at low and high relative humidity. Macrophage phagocytosis was significantly depressed only in mice exposed to the combined pollutants under high relative humidity conditions. This study demonstrates that fine carbon particles can serve as an effective carrier for acidic sulfates, where chemical conversion of adsorbed SO_2 to acid sulfate species occurred. Interestingly, the depression in macrophage function was present as late as 7 days post-exposure. Bolarin et al. (1997) exposed rats to only

50 or 100 ug/m^3 carbon particles in combination with ammonium bisulfate and ozone. Despite 4 weeks of exposure, they observed no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals exposed to the combined pollutants versus ozone alone. Thus, the potential for adverse effects in the lungs of animals challenged with a combined exposure to particles and gaseous pollutants is dependent on numerous factors including the gaseous co-pollutant, concentration, and time.

Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 ug/m^3 H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm ozone in healthy and asthmatic children. The children performed intermittent exercise during the 4-hour exposure to increase the inhaled dose of the pollutants. An overall effect on the combined group of healthy and asthmatic children was not observed. A positive association between acid concentration and symptoms was seen, however, in the subgroup of asthmatic children. The combined pollutant exposure had no effect on spirometry in asthmatic children and no changes in symptoms or spirometry were observed in healthy children. Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less effect on asthmatic children exposed under controlled laboratory conditions in comparison with field studies of children attending summer camp (Thurston et al., 1997). However, prior exposure to H_2SO_4 aerosol may enhance the subsequent response to ozone exposure (Linn et al., 1994; Frampton et al., 1995); the timing and sequence of the exposures may be important. Overall, the evidence suggests that the gaseous-particle interactions of ozone and acidity indicates are more likely to enhance the effects of PM exposures in children than adults, as children playing outdoors would tend to get higher exposures to these air pollution components (as opposed to adults indoors, where acidity and ozone exposure is diminished, relative to the outdoors).

While past acid aerosol research has focused largely on acidity in a particulate form (e.g., as $H_2SO_4^-$), recent research by Peters et al. (1999) as part of the Children's Health Study raises the possibility that the acidity-particle interaction may extend to the interaction of vapor nitric acid (HNO_3) and particles. To study possible chronic respiratory effects of air pollutants, the authors initiated a 10-yr prospective cohort study of Southern California children, with a study design focused on four pollutants: ozone, particulate matter, nitric acid vapor, and nitrogen dioxide (NO_2). Twelve demographically similar communities were selected on the basis of

historic monitoring information to represent extremes of exposure to one or more pollutants. In each community, about 150 public school students in grade 4, 75 in grade 7, and 75 in grade 10 were enrolled through their classrooms. Wheeze prevalence was positively associated with levels of both nitric acid (odds ratio [OR] = 1.45; 95% confidence interval [CI], 1.14-1.83) and NO_2 (OR = 1.54; 95% CI, 1.08-2.19) in boys (who usually spend more time outdoors than girls), and only nitric acid vapor was significant overall for boys and girls. The authors conclude, based on this cross-sectional assessment of questionnaire responses, that current levels of ambient air pollution in Southern California may be associated with effects on schoolchildren's respiratory morbidity. However, it seems unlikely that the highly water soluble HNO_3 could reach deep into the lungs without interaction with particles, much the way that SO_2 has been shown to be picked up by particles entering the lung (Amdur and Chen, 1989; Chen et al., 1992). Thus, it may be that there is a nitric acid-particle interaction that is underlying the nitric acid-child health effects associations reported by Peters and colleagues.

V. IMPLICATIONS OF HEALTH EFFECTS FINDINGS TO THE ADEQUACY OF PM AND SULFATE STANDARDS

The health effects studies documented in this report provide substantial evidence that PM exposures at present ambient levels are adversely affecting the health of children in places throughout the world, including in California. However, whether a PM-health effects association is present or not at a given ambient level is difficult to determine from such studies because, when an effect is not found to be significant, it may be that there is merely insufficient power (e.g., too small a population, or too short a record period) to find an effect that may really be there. Also, such studies tend to be conducted on large populations, where the power is greatest, but where concentrations are also usually highest (i.e., in cities), so studies of low levels are difficult to find. Thus, it is more challenging to evaluate at exactly what pollution exposure concentrations these documented health effects begin to occur for groups of susceptible individuals such as infants and children with asthma.

Probably the best database available at this time for the evaluation of the levels at which pollutants show significant adverse health effects is the body of medical visits and hospital admissions studies, as: 1) they represent a health effect outcome that is clearly adverse, with only long-term illness or death being worse, and; 2) they are reported in large enough numbers to

provide sufficient statistical power, and are statistics that are routinely available for analysis, so there are a large number of studies available to evaluate, as documented in the above sections and the Appendix A Tables. Therefore, these studies will be examined here for insights into the adequacy of the present California standards for the protection of children's health.

The hospital admissions study most directly relevant to the question of the U.S. EPA's $PM_{2.5}$ standard's adequacy is that by Norris and colleagues (1999). As noted in the Appendix A Tables, the estimated mean $PM_{2.5}$ level (based upon nephelometry data) in that study of asthma hospital visits by Seattle children less than 18 was $PM_{2.5}$ = 12 ug/m^3, and the PM association was still significant at these low levels, even after controlling for co-pollutants. This implies that the $PM_{2.5}$ annual average standard should be below 12 ug/m^3 if it is to protect children with asthma. The maximum $PM_{2.5}$ concentration was approximately 7 times this value, above the 65 ug/m^3 24-hr. maximum standard, but the $PM_{2.5}$ short-term standard is as a 3 year average, so that the standard may well also not have been exceeded at this location where acute effects have been documented. These results therefore indicate that the present Federal $PM_{2.5}$ annual standard is not sufficiently protective of children with asthma, and further suggest that the 24-hr maximum may also not be sufficiently protective.

However, the Morgan et al (1998) study of asthma hospital admissions in Sydney, Australia experienced a mean $PM_{2.5}$ = 9.6 ug/m^3, but was unable to detect a significant $PM_{2.5}$ association, despite having larger daily counts and a longer record than the Norris et al (1999) study. This Australian study's results, when compared to the Norris and colleagues study results, suggests that the threshold of $PM_{2.5}$ mass effects on asthma admissions in children is approximately 10 ug/m^3 as an annual mean over several years.

Since the mean PM_{10} concentration during the Norris et al (1999) Seattle study was 21.7 ug/m^3, this study further indicates that the present California PM_{10} annual average standard (30 ug/m^3) is also not sufficiently protective. In the case of PM_{10}, this study's results are confirmed by other studies that have demonstrated significant associations at PM_{10} levels below 30 ug/m^3. As shown in Appendix A, Atkinson et al. (1999a,b) found significant associations with both children's respiratory emergency department (ED) visits and hospital admissions in London, England, where the mean PM_{10} = 28.5 ug/m^3. Similarly, Hajet confirms this result for London doctor's visits for asthma and lower respiratory disease in London, with a mean PM_{10} = 28.2 ug/m^3. Medina et al (1997) also finds significant associations between PM_{13} and doctor's house

calls at PM_{13} mean = 25 ug/m^3. Since PM_{10} is a sub-component of PM_{13}, and will therefore average less than PM_{13}, this Paris study confirms the Norris et al. result that significant adverse health associations occur even at mean PM_{10} below 25 ug/m^3.

Given the results of Norris et al (1999) and confirming PM studies, it is clear that the sulfate standard of 25 ug/m^3 is far from sufficiently protective. The above sulfate health effects section made clear that sulfate is an especially potent component of $PM_{2.5}$, and it's annual average standard should therefore be even lower than that for $PM_{2.5}$. Available studies of sulfates and hospital admissions confirm this conclusion, including the above discussed Burnett (1994) study summarized in Table 6. The average Southern Ontario sulfate level (after eliminating sulfate artifact) was 5.3 ug/m^3, yet significant associations were found between sulfates and children's respiratory admissions, even after controlling for ozone. Analyses of respiratory admissions in Buffalo and New York City (Thurston et al., 1992) at mean levels of 9.3 and 8.9 ug/m^3, respectively, also find significant sulfate-respiratory associations at mean concentrations well below 25 ug/m^3. In addition, examination of the plot of the Ontario data from the Burnett et al. (1994) study (presented above in Figure 8) suggests that the sulfate threshold of effects, if it exists, lies below 5 ug/m^3, perhaps at about 2 ug/m^3. Clearly, the existing California $SO_4^=$ standard is not now sufficiently stringent to protect public health.

VI. CONCLUSIONS

Based upon the above facts and considerations, it is clear that significant adverse health effects can reasonably be expected to occur at present day ambient levels, especially among infants and children, based on the findings of published studies.

Among the factors that cause children to be especially affected by PM air pollution are:

- higher PM exposure concentrations due to greater PM personal cloud than adults;
- higher PM exposure patterns (e.g., more time spent outdoors and greater activity levels);
- higher doses per body weight and lung surface area;
- diminished pollution defenses in infants vs. older children and adults;
- PM exposures may adversely affect body (e.g., lung) development in children;
- higher prevalence of children with asthma than in other age groups,
- larger percentage of children made susceptible by poverty than other age groups; and,
- gas-particle interactions and particle-allergen interactions apparently make pollutants more toxic than they are alone, potentially making the individual pollutant standards not fully protective to susceptible populations, such as children.

Furthermore, an examination of key medical visits and hospital admissions studies conducted at relatively low ambient concentrations evaluated the adequacy of the existing Federal and California PM_{10} and $PM_{2.5}$ mass and sulfate ambient air quality standards. It was found that these standards are not presently sufficiently protective of public health, since significant adverse health impacts have been documented in published studies to occur at ambient levels averaging well below these standards.

However, to help reduce any remaining uncertainties regarding the impacts of PM and sulfates on the health of infants and children, and to determine how to most optimally control such environmental insults, additional research is needed into many aspects of the PM-health effects association among children, including:

- improved identification of the specific characteristics of PM (e.g., ultrafines, acidity, elemental composition, etc.) that are contributing most to noted PM effects, and quantification of their relative roles in PM toxicity;

- further investigation as to whether acute exposures less than one day in length (e.g., 1-hour daily maximum), or longer multi-day exposures (e.g., 2 or more day average PM), also have health importance, over and above that captured by the 24-hour PM peak PM concentration measurement;
- further investigations into particle-gas and particle-allergen interactions;
- animal studies relating increased infection following particle exposure needed, as well as more epidemiological studies of respiratory infections in infants exposed to ambient particles.
- using both experimental and epidemiological methods, conduct further investigations of apparently larger effects of acute and long-term PM exposures on children, and especially infants.

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APPENDIX A - TABLES

Recent Studies Evaluating PM Associations with Medical Visits or Hospital Admissions in Infants and Children

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag,, Excess Risk %, (95% CI=LCI-UCL), Co-Pollutants
Anderson, et al. (1998) London ('87-'92) Population = 7.2 MM BS daily mean = 14.6 ug/m^3 BS 25-75th IQR= 24-38	Poisson regression used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 (mean=19.5/d), 15-64 (mean=13.1/d) and 65+ years (mean =2.6/d).	O_3, SO_2, NO_2, and particles (BS) were all found to have associations with daily hospital admissions for asthma, but there was a lack of consistency across the age groups in the specific pollutant. The BS association was strongest in the 65+ group, especially in winter.	Asthma Admissions. BS=10 ug/m^3 BS Lag = 0-3 day average concentration All age ER= 2.3%(95%CI: 0.2-4.6%) <15yr. ER= 0.88%(95%CI: 1.8-3.7%) 15-64yr ER=0.47%(95%CI: 2.2-3.2%) 65+ yr. ER=8.6%(95%CI: 2.4-15.2%)
Atkinson et al. (1999a) London ('92-'94) Population = NR PM10 Mean = 28.5 ug/m^3 10th-90th IQR =15.8-46.5 ug/m^3 BS mean =12.7 ug/m^3 10th-90th IQR =5.5-21.6 ug/m^3	All-age Respiratory (mean=90/day), Asthma (25.9/day), and Other Respiratory (64.1/day) ED visits analyzed for associations with air pollutants using Poisson methods. Counts for ages 0-14, 15-64, and >64 also examined.	PM_{10} associated, but BS was not, for all-age/all-respiratory category. This may reflect higher toxicity by secondary particles vs. carbonaceous primary particles. PM_{10} results driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship.	PM_{10} (30.7 ug/m^3) No co-pollutant: All Respiratory ED visits All age(lag 1d)ER=3.0%(95%CI:0.8-5.2%) <15yrs(lag 2d)ER=3.9%(95%CI: 0.6-7.3%) 15-64yr(lag1d)ER=5.2%(95%CI:2.1-8.4%) Asthma ED visits All age(lag 1d)ER=5.4%(95%CI:1.8-9.0%) <15yrs (lag 2d)ER=7.4%(95%CI:2.1-13%) 15-64yr.(lg 1d)ER=7.8%(95%CI:2.8-13%)
Atkinson et al. (1999b) London ('92-'94) Population = 7.2 MM PM_{10} Mean = 28.5 ug/m^3 10th-90th IQR=15.8-46.5 ug/m^3 BS mean=12.7 ug/m^3 10th-90th IQR=5.5-21.6 ug/m^3	All-age Respiratory (mean=150.6/day), all-age Asthma (38.7/day), COPD plus Asthma in adults >64 (22.9/day), and lower Respiratory (64.1/day) in adults >64 (16.7/day) hospital admissions from London hospitals considered. Counts for ages 0-14, 15-64, and >64 also examined.	Positive associations were found between emergency hospital admissions for respiratory disease and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} were included simultaneously, the size and significance of each was reduced.	PM_{10} (30.7ug/m^3), no co-pollutant. All Respiratory Admissions: All age(lag 1d)ER=3.0%(95%CI:1.1-4.9%) 0-14 y (lag 1d)ER=4.9%(95%CI:2.1-7.7%) 15-64y(lag 2d)ER=4.2%(95%CI:2.6-7.3%) 65+ y.(lag 3d)ER=3.0%(95%CI:0.47-5.6%) Asthma Admissions: All age(lg 3d)ER=2.1%(95%CI: 1.1-5.4%) 0-14 y (lag 3d)ER=3.3%(95%CI: 0.7-7.5%) 15-64 y(lag 3d)ER=5.7%(95%CI:0.7-11.%) 65+ y.(lag 0d)ER=7.2%(95%CI: 1.25-16%)

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag,, Excess Risk %, (95% CI=LCI-UCL), Co-Pollutants
Braga et al. (2000?) Author Affiliation: Non-Profit Research Funding: Public Sao Paulo, Brazil ('92-'93) Population = NR PM_{10} mean = 66.3 ug/m^3 PM_{10} Std. Deviation = 26.1 PM_{10} Min./Max. = 26.7/165.4	Pediatric (<13 yrs.) hospital admissions (mean=67.6/day) from public hospitals serving 40% of the population were regressed (using both Poisson and maximum likelihood methods) on pollutants, controlling for month of the year, day-of-week, weather, and the daily number of non-respiratory admissions (mean=120.7/day). Pollutants considered included PM_{10}, O_3, SO_2, CO, and NO_2.	PM_{10} and O_3 were the two pollutants found by the authors to exhibit the most robust associations with respiratory HA's. SO_2 showed no correlation at any lag. Simultaneous regression of respiratory HA's on PM_{10}, O_3, and CO decreased effect estimates and their significance, suggesting that "there may not be a predominance of any one pollutant over the others". No safe threshold was found for PM_{10} or O_3. Associations are ascribed primarily to auto emissions by the authors.	PM_{10} (66.3 ug/m^3), no-co-pollutant Respiratory Hospital Admissions (<13 yr.) (0-5 day lg avg.)ER=12%(95%CI:6.1-18%)
Delfino et al., 1997 Montreal,Canada (6-9/92,6-9/93) Population = 3 million 1993 Means (SD): PM_{10}= 21.7 ug/m^3 (10.2) $PM_{2.5}$= 12.2 ug/m^3 (7.1) $SO_4^=$= 34.8 nmol/m^3 (33.1) H^+= 4 nmol/m^3 (5.2)	Association of daily respiratory ED visits (mean = 98/day from 25 of 31 acute care hospitals) with O_3, PM_{10}, $PM_{2.5}$, $SO_4^=$, and H^+ assessed using linear regression with controls for temporal trends, auto-correlation, and weather. Five age sub-groups considered.	No associations with ED visits in '92, but 33% of the PM data missing then. In '93, only H^+ associated for children <2, despite very low H^+ levels. F^+ effect stable in multiple pollutant models and after excluding highest values. No associations for ED visits in persons 2-64 yrs. of age. For patients >64,O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ were all positively associated with visits ($p < 0.02$), but PM effects smaller than for O_3.	Respiratory ED Visits Children <2 yrs: (H^+ lag = 2 day) 4 nmol/m^3 H^+ ER= 5.0% (CI = 0.4-9.6%) Adults >64: (pollutant lags = 1 day) 21.7 ug/m^3 PM_{10} ER= 16% (CI = 4-28%) 12.2 ug/m^3 $PM_{2.5}$ ER= 12% (CI = 2-21%) 34.8 nmol.m^3 $SO_4^=$ ER= 6% (CI = 1-12%)
Gouveia et al (2000) Author Affiliation: Non-profit Research Funding: Public Study Period.:'92-'94 Sao Paulo, Brazil Population = 9.5 MM x 66% PM_{10} mean = 64.9 ug/m^3 PM_{10} IQR = 42.9-75.5 ug/m^3 PM_{10}10/90th%ile=34.5/110ug/m^3 PM_{10} 95th%ile = 131.6 ug/m^3	Daily public hospital admissions for respiratory diseases by children (mean Resp. < 5y = 56.1/d; mean Pneumonia <5y =40.8/d; mean asthma <5 y = 8.5/d; mean Pneum.<1y=24.0) and daily levels of weather and air pollutants (PM_{10}, SO_2, NO_2, O_3, and CO) were analyzed with Poisson regression. PM_{10} measured by Beta-gauge.	Children's HA's for total respiratory and pneumonia gave positive associations with O_3, NO_2, and with PM_{10}. Effects for pneumonia greater than for all respiratory diseases. Effects on infants (<1 yr. old) gave higher estimates. Similar results for asthma, but estimates higher than for other causes. Results noted to agree with prior publications, but smaller RR's. This may be an artifact of higher baseline admission rates in this poor sub-population vs. other studies, but this is not intercompared by the authors.	For PM 10th-90th %ile ?=75.5 ug/m^3: All Respiratory HA's for children < 5yrs. ER = 4.0% (95% CI = ¯1.5%, 9.9%) Pneumonia HA's for children <5 yrs. ER = 5.0% (95% CI = ¯1.6%, 12.1%) Asthma HA's for children <5 yrs. ER = 5.2% (95% CI = ¯7.7%, 19.8%) Asthma HA's for children <1 yrs. ER = 9.4% (95% CI = 1.3%, 18.0%)

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ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Hajet et al., 1999 London, England (92'-'94) Population = 282,000 PM_{10} mean = 28.2 ug/m^3 PM_{10} 10^{t}-90^{th}%=16.3-46.4 ug/m^3 BS mean = 10.1 ug/m^3 BS 10^{t}-90^{th}%=4.5-15.9 ug/m^3	Examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care GP asthma and "other LRD" consultations [asthma means = 35.3 (all ages); = 14.(0-14 yrs,); = 17.7 (15-64 yrs.); = 3.6 (>64 yrs.)] [LRD means = 155. (all ages); = 39.7(0-14 yrs,); = 73.8 (15-64 yrs.); = 41.1 (>64 yrs.)], Time-series analyses of daily numbers of GP consultations were performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, were observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children.. Across all of the various age, cause, and season categories considered in this research, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	<u>Asthma Doctor's Visits</u>: 30 ug/m^3 PM_{10} (10-90^{th} %ile Range) -Year-round, Single Pollutant: All ages (lg 2): ER=3.2% (CI=-0.4-6.8%) 0-14 yrs.(lg 1): ER=3.8% (CI=1.0-8.8%) 15-64 yrs.(lg 0): ER=5.4% (CI=1.6-9.2%) >64yrs.(lg 2): ER=7.1% (CI=-1.1-16%) <u>Other Lower Resp. Dis. Doctor's Visits</u>: 30 ug/m^3 PM_{10} (10-90^{th} %ile Range) -Year-round, Single Pollutant: All ages (lg 2): ER=2.1% (CI=-0.4-3.8%) 0-14 yrs.(lg 1): ER=2.5% (CI=-0.7-5.8%) 15-64 yrs.(lg 2): ER=2.2% (CI=0.0-4.5%) >64yrs.(lg 2): ER=3.7% (CI=-0.3-7.2%)
Lin CA, et al, 2000 Author Affiliation: Non-profit Research Funding: NR Sao Paulo, BR ('91-'93) Population = NR PM_{10} mean =65 ug/m^3 PM_{10} SD = 27 ug/m^3 PM_{10} range = 15-193 ug/m^3	Respiratory ED visits by children (0-12 yrs.) to a major pediatric hospital (mean = 56/day) related to PM_{10}, SO_2, NO_2, CO, and O_3 using Gaussian linear regression modeling, Poisson modeling, and a polynomial distributed lag model. Lower Respiratory (mean = 8/day) and Upper Respiratory (mean = 39/day) ED visits, and visits due to Wheezing (mean=9/day), evaluated.	PM_{10} was found to be "the pollutant that exhibited the most robust and stable association with all categories of respiratory disease". O_3 was the only other pollutant that remained associated when other pollutants were all added to the model simultaneously. However, some pollutant coefficients went negative in multiple pollutant regressions, suggesting coefficient intercorrelations in the multiple pollutant models.	For 10 ug/m^3 PM_{10} (0-5 day lag mean) <u>Respiratory ED Visits(<13 yrs.)</u> Single Pollutant Model: PM_{10} ER=4.0% (CI=3.4%-4.6%) All-Pollutant Model: PM_{10} ER=5.2% (CI=4.0%-6.5%) <u>Lower Respiratory ED Visits (<13 yrs.)</u> Single Pollutant Model: PM_{10} ER=4.2% (CI=2.4%-6.0%) All-Pollutant Model: PM_{10} ER=8.0% (CI=5.0%-11%)
Medina et al., 1997 Greater Paris '91-'95 Population = 6.5 MM Mean PM_{13} = 25 ug/m^3 PM_{13} min/max = 6/95 ug/m^3 Mean BS = 21 ug/m^3 BS min/max = 3/130 ug/m^3	Evaluated short-term relationships between PM_{13} BS air pollution and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris using Poisson regression.	A relationship between all age (0-64 yrs.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable.	<u>Doctor's Asthma House Visits</u>: 10 to 50 ug/m^3 PM_{13}:5-95^{th}%ile Increment Year-round, Single Pollutant: All ages (lg 2): ER=10% (CI=4-18%) 0-14 yrs.(lg 0-3): ER=32% (CI=16-51%) 15-64 yrs.(lg 2): ER=5% (CI=-5%-13%)

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Moolgavkar, et al (2000b) Author Affiliation: Non-profit Research Funding: Industry Study Period: 1987-1995 <u>Los Angeles (LA County), CA</u> Population = NR PM_{10} median = 44 ug/m^3 PM_{10} IQR= 33-59 ug/m^3 $PM_{2.5}$ median = 22 ug/m^3 $PM_{2.5}$ IQR = 15-31 ug/m^3	Investigated associations between air pollution and COPD HA's in LA, for children 0-19 (med.=17/d), adults 20-64 (med.=24/d), and adults 65+ (med. = 20/d). Used Poisson GAM's controlling for day-of-week, season, and splines of temperature and RH (but not their interaction) adjusted for overdispersion. Co-pollutants were O_3, SO_2, NO_2, and CO. PM data available only every 6th day, vs. every day for gases.	PM was associated with admissions in single pollutant models, but not in two pollutant models. Analysis in 3 age groups in LA yielded similar results. Author concludes that "the gases, other than ozone, were more strongly associated with COPD admissions than PM, and that there was considerable heterogeneity in the effects of individual pollutants in different geographic areas".	Most Significant Positive ER (t-statistic) Single Pollutant Models: <u>LA COPD HA's</u> (25 ug/m^3 PM_{10}, 10 ug/m^3 $PM_{2.5}/PM_{2.5-10}$) (0-19 yrs.): PM_{10} lg2=5.2% (t=3.4) (0-19 yrs.): $PM_{2.5}$ lg0=1.7% (t=1.9) (0-19 yrs.): $PM_{2.5-10}$ lg2=6.5% (t=4.3) (20-64 yrs.): PM_{10} lg2=3.2% (t=2.7) (20-64 yrs.): $PM_{2.5}$ lg2=2.2% (t=3.0) (20-64 yrs.): $PM_{2.5-10}$ lg2=3.5% (t=3.0) (>64 yrs.): $PM_{2.5-10}$ lg3=2.0% (t=1.8)
Morgan et al, 1998 Author Affiliation: Non-profit Research Funding: Public Sydney, AU ('90-'94) Population = NR $PM_{2.5}$ 24h. mean = 9.6 ug/m^3 $PM_{2.5}$ 10^{th}-90^{th}% =3.6-18 ug/m^3 $PM_{2.5}$ max-1h. mean=22.8ug/m^3 $PM_{2.5}$ 10^{th}-90^{th}%=7.5-44.4ug/m^3	A Poisson analysis, controlled for overdispersion and autocorrelation via GEE, of asthma (means: 0-14 yrs.=15.5/day; 15-64=9/day)), COPD (mean 65+yrs. =9.7/day), and heart disease HA's. $PM_{2.5}$ estimated from nephelometry. Season and weather controlled using dummy variables.	Childhood asthma was primarily associated with NO_2, while COPD was associated with both NO_2 and PM. 1-hr. max $PM_{2.5}$ more consistently positively related to respiratory HA's than 24-h avg $PM_{2.5}$. Adding all other pollutants lowered PM effect sizes, although pollutant inter-correlations makes many pollutant model interpretations difficult. No association found between asthma and O_3 or PM.	<u>Asthma HA's</u> Single Pollutant Model: For 24h $PM_{2.5}$ 10^{th}-90^{th}% =3.6-18 ug/m^3 1-14 yrs.(lag1) ER= -0.87%(CI=˜4.6 - 3.0) 15-64 yrs.(lag0) ER=1.31%(CI=˜2.3 - 5.1) For 1h $PM_{2.5}$ 10^{th}-90^{th}% =7.5-44.4 ug/m^3 1-14 yrs.(lag1) ER= -0.87%(CI=˜4.6 - 3.0) 15-64 yrs.(lag0) ER=1.31%(CI=˜2.3 - 5.1) Multiple Pollutant Model: For 24h $PM_{2.5}$ 10^{th}-90^{th}% =3.6-18 ug/m^3 1-14 yrs.(lag1) ER= -0.35%(CI=˜4.3 - 3.8)
Norris et al (1999) Author Affiliation: Non-profit Research Funding: Public Seattle, WA (9/95-12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.7 ug/m^3 PM_{10} IQR = 11.6 ug/m^3 ϑ_{sp} mean = 0.4 $m^{-1}/10^{-4}$ (˜12.0 ug/m^3 $PM_{2.5}$) ϑ_{sp} IQR = 0.3 $m^{-1}/10^{-4}$ (˜9.5 ug/m^3 $PM_{2.5}$)	The association between air pollution and childhood (<18 yrs.) ED visits for asthma from the inner city area with high asthma hospitalization rates (0.8/day, 23/day/10K persons) compared with lower hospital use areas (1.1/day, 8/day/10K persons). Daily ED counts were regressed against PM_{10}, light scattering (ϑ_{sp}), CO, SO_2, and NO_2 using a semiparametric Poisson regression model evaluated for over-dispersion and auto-correlation.	Associations found between ED visits for asthma in children and fine PM and CO. CO and PM_{10} highly correlated with each other (r=.74) and K, an indicator of woodsmoke pollution. Considering baseline risks/10K population indicates a higher PM attributable risk (AR) in the inner city. These findings were seen even though the mean estimated $PM_{2.5}$ concentration was below the newly adopted annual National Ambient Air Quality Standard of 15 ug/m^3.	<u>Children's (<18 yrs.) Asthma ED Visits</u> Single Pollutant Models: For 24h PM_{10} IQR =11.6 ug/m^3 Lag1 ER= 14% (CI= 8% - 23%) For 24h ϑ_{sp} IQR =0.3 $m^{-1}/10^{-4}$ (˜9.5 ug/m^3 $PM_{2.5}$) Lag1 ER= 15% (CI= 8% - 23%) Multiple Pollutant Models: For 24h PM_{10} IQR =11.6 ug/m^3 Lag1 ER= 14% (CI= 4% - 26%) For 24h ϑ_{sp} IQR=0.3 $m^{-1}/10^{-4}$ (˜ 9.5 ug/m^3 $PM_{2.5}$) Lag1 ER= 17% (CI= 8% - 26%)

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ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Norris et al (2000) Author Affiliation: Non-profit Research Funding: Public <u>Spokane, WA</u> (1/95—3/97) Population = 300,000 PM_{10} mean. =27.9 ug/m^3 PM_{10} Min/Max=4.7/186.4 ug/m^3 PM_{10} IQR = 21.4 ug/m^3 <u>Seattle, WA</u> (9/95—12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.5 ug/m^3 PM_{10} Min/Max = 8/69.3 ug/m^3 PM_{10} IQR = 11.7 ug/m^3	Associations investigated between an atmospheric stagnation index (# of hours below median wind speed), a "surrogate index of pollution", and asthma ED visits for persons <65 yrs. (mean=3.2) in Spokane and for children <18 (mean=1.8) in Seattle. Poisson GAM modeling, controlled for day of week, long-wave effects, and temperature and dew point (as non-linear smooths). Factor Analysis (FA) applied to identify PM components associated with asthma HA's.	Stagnation persistence index was strongly associated with ED visits for asthma in 2 cities. FA indicated that products of incomplete combustion (especially wood-smoke related K, OC, EC, and CO) are the air pollutants driving this association. Multi-pollutant models run with Stagnation as the "co-pollutant" indicated the importance of general air pollution over any single pollutant index, but provided no indication of the importance of the various pollutants relative to each other.	<u>Asthma ED Visits</u> Single Pollutant Models Persons<65 years (Spokane) For PM_{10} IQR = 21.4 ug/m^3 Lag 3 ER = 1% (95% CI= ¯5% - 7%) Persons<18 years (Seattle) For PM_{10} IQR = 11.7 ug/m^3 Lag 3 ER = 11% (95% CI= 2% - 20%)
Ostro et al (1999) Author Affiliation: Non-profit Research Funding: World Bank Santiago, CI (7/92—12/93) <2 yrs. Population ˜ 20,800 3-14 yrs. Population ˜ 128,000 PM_{10} mean. =108.6 ug/m^3 PM_{10} Min/Max=18.5/380 ug/m^3 PM_{10} IQR = 70.3 – 135.5 ug/m^3	Analysis of daily visits to primary health care clinics for upper or lower respiratory symptoms by children 2-14 years of age (mean LRS=111.1/day) and < age 2 (mean LRS=104.3/day). Daily PM_{10} and O_3 and meteorological variables considered. The multiple regression GAM included controls for seasonality (LOESS smooth), temperature, day of week, and month.	Analyses indicated an association between PM_{10} and medical visits for LRS in children ages 2-14 and in children under age 2. PM_{10} was not related to non-respiratory visits (mean =208/day). Results unchanged by eliminating high PM_{10} (>235 ug/m^3) or coldest days (<8°C). Adding O_3 to the model had little effect on PM_{10}-LRS associations.	<u>Lower Resp. Symptoms Clinic Visits</u> PM_{10} IQR = 50 $^{ug/m3}$, One Poll. Model: -Children<2 years Lag 3 ER = 2.5% (95% CI= 0.2% - 4.8%) -Children 2-14 years Lag 3 ER = 3.7% (95% CI=0.8% - 6.7%) Two Pollutant Models (with O_3): -Children<2 years Lag 3 ER = 2.2% (95% CI= 0% - 4.4%) -Children 2-14 years Lag 3 ER = 3.7% (95% CI=0.9% - 6.5%)
Rosas, et al (1998) Author Affiliation: Non-profit Research Funding: public SW Mexico City ('91) Population = NR PM_{10} mean. =77 ug/m^3 PM_{10} min/max= 25/183 ug/m^3	Log-regression analysis of the relationships between emergency admissions for asthma to a hospital for children <15 years (mean=2.5/day), adults (mean=3.0/day), and older adults >59 years (mean=0.65/day) and lag 0-2 average pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. Long wave controlled only by separating the year into two seasons: "dry" and "wet". Day-of-week not included in models.	There were few statistical associations found between asthma admissions and air pollutant. Grass pollen was associated with child and adult admissions, and fungal spores were associated with child admissions. The authors conclude that aeroallergens may be more strongly associated with asthma than air pollutants, and may act as confounding factors in epidemiologic studies. Results are limited by low power and the lack of long-wave auto-correlation controls in the models.	NR

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ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Sunyer et al (1997) Barcelona ('86-'92) BS Median: 40 ug/m^3 BS Range: 11-258 (B Helsinki ('86-'92) BS Median: - BS Range: - Paris ('86-'92) BS Median: 28 ug/m^3 BS Range: 4-186 ug/m^3 London ('86-'92) BS Median: 13 ug/m^3 BS Range: 3-95 ug/m^3	Daily counts of asthma HA's and ED visits in adults [ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (H); 7.3 (P)] and children [ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)] related to BS, SO_2, NO_2, and O_3 air pollution. Asthma (ICD9=493) studied in each city, but the outcome examined differed across cities:	In children, daily admissions increased significantly with SO_2 and positively (but non-significantly) with Black Smoke and NO_2, though the latter only in cold seasons. No association was observed in children for O_3. The weakness of PM in these analyses may be result of the use of the BS index, a measure of only the primary carbonaceous particles, which may be less toxic than other (i.e., secondary) aerosols.	ER per 50µg/m^3 BS (24 h Average) <u>Asthma Admissions/Visits</u>: <15 yrs.: London ER = 3.1% (lg 0d) Paris ER = 3.0% (lg 2d) Total ER = 3.0% (95%CI: ¯2.1%-8.4%) 15-64 yrs: Barcelona ER = 3.6% (lg 3d) London ER = 3.5% (lg 0d) Paris ER = 1.2% (lg 0d) Total ER = 2.1% (95%CI: ¯1.5%-5.9%)
Wong, et al (1999) Study Period.:'94-'95 Hong Kong Population = NR PM_{10} mean = 50.1 ug/m^3 PM_{10} median = 45.0 ug/m^3 PM_{10} IQR = 30.7, 65.5 ug/m^3	Poisson regression applied to assess association of daily NO_2, SO_2, O_3, and PM_{10} with emergency HA's for all respiratory (median = 131/day) and COPD (median = 101/day) causes. Effects by age groups (0-4, 5-64, and 65+ yrs.) also evaluated.	Positive associations were found for HA's for all respiratory diseases and COPD with all four pollutants. PM_{10} results for lags 0-3 cumulative. Admissions for asthma, pneumonia, and influenza were associated with NO_2, O_3, and PM_{10}. Those aged > or = 65 years were at higher risk, except for PM_{10}.	PM_{10} ? = 10 ug/m^3 (Lags = 0-3 days) <u>Respiratory HA's</u> All age: ER= 1.6% (95%CI: 1.0, 2.2%) 0-4yrs.: ER= 1.9% (95%CI: 1.1, 2.8%) 5-64yrs.: ER= 1.7% (95%CI: 0.9, 2.6%) 65+ yrs.: ER= 1.8% (95%CI: 1.0, 2.6%)

APPENDICES SUBMITTED BY WSPA WITH THEIR COMMENTS:

APPENDIX 1:

CANCER UNIT RISK

OEHHA Position: Diesel PM (DEP) is a carcinogen and a unit lung cancer risk can be calculated using the Garshick study of railroad workers.

The Garshick et al. Study is not appropriate for a quantitative risk assessment (QRA) because of inadequate estimates of exposure, loss of workers in the latter years of follow-up, negative exposure-response based on years exposed, and latency period is too short for many lung cancers to have been caused by diesel exposure.

Several cohort studies of lung cancer and ambient PM air pollution have been suggested as supporting the idea that diesel PM (DEP) is a carcinogen. The two major cohort studies (Six Cities, American Cancer Society) do not show increased risk of lung cancer associated with PM, and therefore do not support the hypothesis that ambient PM (or ambient diesel PM) increases the risk of lung cancer.

As correctly noted by the authors, all of the human studies evaluating carcinogenic potential of DEP are on adults. In the animal studies exposures were initiated when the animals were young adults. However, carcinogenicity was observed only at exposure levels producing particle overload. So, there is no direct experimental evidence cited, or available, to support the assertion that DEP produces differentially higher carcinogenicity potential in children.

PAHs are the constituents most likely contributing to any carcinogenicity potential associated with DEP. However, simply noting that certain PAHs produce DNA adducts does not establish either carcinogenicity or differential susceptibility.

Some specific comments on mechanism of carcinogenicity (including discussion of the animal carcinogenicity findings) were responded to specifically by OEHHA in Appendix C Vol 3.1 of the TAC document, and the reader is referred to that source for further details.

OEHHA discusses the issue of cancer risk for children in Section IV (page 38 et seq.) of the introduction to the prioritization document. This is an area in which further research is needed, and OEHHA intends to give this issue further consideration at later stages of the SB25 process. Since most of the quantitative data on diesel exhaust is from occupational exposures, it is unfortunately (from the analyst's viewpoint) inevitable that there is little direct evidence available on age-related carcinogenic effects of diesel exhaust.

Specific Comments on Carcinogenicity

OEHHA Position: Unit Risk based on RR Workers Study (Garshick et al.). Based on the Garshick et al. (1987, 1988) study of railroad workers, OEHHA reported a cancer unit risk factor

of 1.3E-4 to 1.5E-3/ug/m^3 measured as PM. Diesel exhaust was considered a lung carcinogen based primarily on reviews by Lipsett and Campleman (1999) of 30 eligible occupational studies and HEI (1995) of more than 35 occupational studies and using criteria for causal inference from epidemiological studies. OEHHA suggested the relationship between occupational diesel exhaust exposure and lung cancer could not be attributed to potential confounding by cigarette smoke.

Comment: In an analysis of diesel studies for quantitative risk assessments (QRA), HEI (1999) concluded that the Garshick et al. Study of railroad workers "has very limited utility for QRA of lifetime lung cancer risk from exposure to ambient levels of diesel exhaust." Some reasons this study is not useful for QRA are summarized.

1. *The exposure data is inadequate because it is based on current levels and not on exposures that occurred during the study period and confounding exposures were not adequately dealt with. Exposure was only adequate for a crude categorical classification by job class but not for a quantitative exposure-response analysis by years in a job, intensity (ug/m^3) or cumulative exposure (ug/m^3-years) (HEI, 1999).*

2. *The evidence for a positive association rests entirely on differences in risks among job categories. However, within all job categories there was a negative association with years worked. A negative exposure-response trend was also observed based on quantitative measures of cumulative exposure (Crump, 1999). The differences by job category could be due to differences in lifestyle, as the most highly exposed job category did not have a significantly increased risk or the highest risk of lung cancer (HEI, 1999).*

3. *The follow-up in the last 4 years (and perhaps years before that) was incomplete. If those four years are not included in the analysis, then the maximum latency is only 17 years. This latency is too short to adequately estimate risk of lung cancer. A study with this short a latency period should be excluded because many of the lung cancer have too short a latency to have been plausibly caused by diesel exhaust exposure.*

4. *HEI (1999), Crump (1999) and Clean Air Scientific Advisory Committee (CASAC) of the Environmental Protection Agency (EPA) recommend that this study not be used for a QRA. It was not possible to accurately reconstruct past exposures or even to determine when actual diesel exposure began because of the gradual introduction of diesel engines over time.*

APPENDIX 2:

DIESEL EXHAUST AS A LUNG CARCINOGEN

OEHHA Position: Three reviews were cited to support the claim that occupational exposure to diesel exhaust is a lung carcinogen (Lipsett and Campleman, 1999; (Bhatia et al., 1998; HEI, 1995).

Specific Comments

Occupational exposures are generally higher than ambient concentrations, ranging from about 4 to 1700 ug/m^3 daily exposure. Highest exposures were in enclosed spaces such as mines. In general workplace exposures are several orders of magnitude higher than the outdoor ambient concentrations (Watts, 1995).

1. HEI (1995) suggests that occupational exposure to diesel exhaust is associated with increased risk of lung cancer, and that several cohort mortality studies indicate exposure to air pollution from fossil fuel combustion is also associated with increased lung cancer rates independent of smoking and occupation (Dockery et al., 1993; Pope et al., 1995; Mills et al., 1991). Therefore, HEI (1995) concluded diesel exhaust in air pollution might also increase the risk of lung cancer.

   However further analysis of the Six Cities and American Cancer Society (ACS) PM studies does not provide support for an association of lung cancer associated with fine PM (which includes traffic-related PM). The HEI reanalysis of the Six Cities and ACS cohorts did not show any increased risk of lung cancer (Krewski et al., 2000). For example the RR in Six Cities was 1.03 (0.75-1.41) per 10 ug/m^3 increase in $PM_{2.5}$ using the extended model and alternative indices for occupational exposure. In the ACS study the RR was 1.00 (0.91-1.11) per 10 ug/m^3 increase in $PM_{2.5}$ using the model with calendar year time axes. The AHSMOG study (Mills et al., 1991) has been updated and showed an increased risk of lung cancer mortality among males of 1.65 (1.21-2.27) but not females with a RR of 1.13 (0.81-1.57) per 10 ug/m^3 increase in PM_{10} (Abbey et al., 1999). Nyberg et al. (2000) used NO_2 as a surrogate measure for road traffic in Stockholm and found a nonsignificant RR of 1.17 (0.84-1.62) for the top 90% of exposures estimated for the past 30 years. The only significant finding was an association with a 20-year lag, which could be a chance finding given the large number of comparisons.

   Thus the air pollution data do not provide consistent or convincing support for the idea that lifetime exposure to fine PM (of which diesel particulate is a part) poses a significant increased risk of lung cancer.

2. A problem with the studies of diesel exhaust effects among railroad workers and truck drivers is that there has been a continuous increase in the use of diesel engines. The studies of these workers have estimated that 1959 is the point in time where there was 100% use of diesel engines in the railroads (Garshick et al., 1987) and majority of heavy duty trucks had diesel engines (Steenland et al., 1998) (or 1960 in Steenland et al., 1990). There was diesel

exposure before 1959 for some but not all individuals, but the analyses could not determine for whom. As a result diesel exposure was underestimated for those exposed before the 1959 date. This can produce an overestimate of the risk.

3. A second related issue is with regard to latency. Maximum latency using the 1959 cutoff data is 21 years for railroad workers and 22 years for teamsters. For an entire study cohort a maximum latency period of this short length is unsatisfactory. Estimating a plausible risk of lung cancer from an occupational exposure should allow a minimum latency of 20 or more years. The National Research Council (NRC-NAS, 1981) suggested a prospective study needs to cover perhaps 30-40 years, which should take care of the long latency period between first exposure to a carcinogen and subsequent development of cancer. Studies with less than 20-years since first exposure for a substantial proportion of the cohort will not have a latency period long enough to assess lung cancer risk from diesel exposure. HEI (1995) noted that the railroad study by Garshick et al. (1988) did not analyze the data by latency, and because decades may be required to manifest lung cancer it is difficult to draw firm conclusions about the magnitude of the risk.

4. The NRC noted that because of the much greater risk of cigarette smoking than from diesel exhaust it is important to consider adequately the extent of smoking. Three review suggested the increased risk of lung cancer could not be attributed to confounding from cigarette smoke (Bhatia et al., 1998; HEI, 1995; Lipsett and Campleman, 1999). But others have a contrary point of view with respect to both causality and control of smoking (Stober and Abel, 1996; Muscat and Wynder, 1995). Some of this uncertainty can be reduced by establishing quantitative exposure-response relationships (NRC-NAS, 1981). It would be helpful to acknowledge that there is no a monolithic view regarding diesel or ambient PM as carcinogens.

5. There are two additional occupational studies of lung cancer not considered by OEHHA. These are cohort mortality studies of coal miners (Johnston et al., 1997) and potash miners (Saverin et al., 1999) with internal analyses comparing exposed to nonexposed miners. While these studies also have short latencies, the estimates of cumulative exposure are based on precise and documented dates when diesel exposure actually began and so do not have the uncertainty regarding individual-level latency found in the studies of railroad and truck driver cohorts.

The miners in these studies are exposed to measured diesel PM well above ambient levels and the results are not consistent with an increased risk of lung cancer. In addition, estimation of lifetime risk associated with ambient levels of 1 ug/m^3 diesel PM indicate no increased risk of lung cancer, total mortality, or respiratory mortality (Gamble and Nicolich, 2000). These studies with quantitative estimates of exposure to diesel exhaust do not support a causal association for lung cancer, and do not support an increased risk of lung cancer at levels common in ambient air. However, both studies have some workers with short latency and there was no stratification to remove workers with short latencies.

Johnston et al. (1997) investigated the association between lung cancer and exposure to respirable diesel exhaust particulate in a cohort of British coalminers. The cohort consisted of

18,166 miners employed in 10 collieries. Diesels were introduced into 6 of the mines in the early 1950's to mid 1980's. The primary estimate exposure was based on respirable particulate mass measurements collected at (approximately) 5-year intervals at each colliery. A proportion of total respirable particulate was estimated to be diesel particulate based on combustible and quartz content of the total respirable samples. Average shift concentrations of combustible diesel particulate ranged from about 3 to 370 ug/m^3. Lifetime average exposure ranged from close to none to about 19 ug/m^3 in coalmines using diesels.

The SMR was 0.86 (0.80-0.93) for lung cancer (Miller et al., 1997). The UR per ug/m^3 diesel PM was estimated as 0.985 (0.9979-0.9928) for lung cancer. Lung cancer exposure-response relationships were investigated using Cox regression models and included terms for age, smoking, and entry into the cohort. After adjustment for pit differences, the diesel exposure variables were not significant in either the 15 year lagged model or unlagged model. In the unlagged model the RR for diesel exhaust was 0.98 (0.78-1.33) per 1 ug/m^3 combustible respirable coalmine dust, or 0.86 per 1 ug/m^3 total respirable particulate. Some workers in this study have short latencies which could explain no significant exposure-response trends. Saverin et al. (1999) studied 5981 male potash miners in Germany who had worked at least 1-year underground after 1969; 55% were exposed before 1970. The cohort was followed from 1970-1994. Mobile diesel powered vehicles were used in the mines between 1969 and 1991 when the mines closed for a maximum of 22 years possible exposure to diesel exhaust. Concentrations ranged from 0.04 to 1.28 mg/m^3 total carbon. Lifetime average intensities were estimated to be 3.6-93 ug/m^3 total carbon. About half of the miners had a cumulative exposure of 3000 ug/m^3-years, or a lifetime intensity of 43 ug/m^3. There were no large differences in smoking patterns between exposure categories with intervals of 0.5 mg/m^3-yrs, so smoking was not considered a confounder. There were 38 lung cancer cases with an SMR of 0.78. With an average lifetime intensity of 43 ug/m^3 for the total cohort, the RR at 1 ug/m^3 estimated from the SMRs is 0.9942 (0.9862-1.0016) for lung cancer. The Mantel-Haenzel analyses showed no significant E-R trend of diesel exhaust associated with lung cancer with a risk of 1.02 (0.99-1.06). The E-R trend estimated by regression for the total cohort was 1.00743 (0.98985-1.02542) for lung cancer. The URs per 1 ug/m^3 in the subcohort was 1.0143 (0.9907-1.0385) for lung cancer.

APPENDIX 3:

PM STUDIES OF NONCANCER EFFECTS

OEHHA Position: OEHHA notes that the particles in diesel exhaust are considered the most likely agents causing the noncancer effects. PM in ambient air has been associated with respiratory effects including symptoms, decline in lung function, increased hospital admissions and increased mortality during severe air pollution episodes. OEHHA suggests that "diesel exhaust is a significant contributor [to ambient PM] in many urban areas." Evidence is also cited that diesel PM enhances allergic responses. The evidence regarding these conclusions will be reviewed.

Comment: In sum, these time-series studies suffer from several problems that limit their usefulness in asserting that DEP causes increased mortality and hospital admissions:

- *Exposures are group-level so no individual-level exposure to any pollutant is known, and there is not even group-level measurement of DEP.*

- *Ambient PM is not always significantly associated with an adverse health effect.*

A number of time-series air pollution studies are cited by OHHEA. These studies are completely based on group-level exposure data routinely collected at central monitoring stations. Each individual in the metropolitan area(s) is assigned the same exposure. None of the studies use a surrogate such as elemental carbon to estimate the proportion of diesel PM in the pollutant mixture. The proportion of diesel PM is not a constant but varies within and between cities, so the exposure-response relationships estimated for PM_{10} or $PM_{2.5}$ or sulfate will not reliably represent a valid association for diesel PM. If the associations are stronger for ozone than for PM, then the relationship between diesel PM and health effects in air pollution studies becomes even more speculative. Without some rationale beyond the assertion that diesel PM comprises a significant proportion of ambient PM, the conclusion of causal association between ambient diesel PM and respiratory morbidity and mortality is also speculative.

OEHHA Position of DEP and Linkage to PM Air Pollution: The statewide average diesel PM concentration is estimated to be 3.2 ug/m^3, ranging from 0.3 ug/m^3 to 3.6 ug/m^3.

Comment: A question the OEHHA has not addressed is the meaning of a significant contribution of diesel PM to total ambient PM. It is not clear that a contribution of less than 10% of ambient PM is biologically significant and sufficient to cause the exacerbation of asthma and respiratory effects being attributed to this particulate source. This question is important because there are few, if any, studies of the effect of diesel PM per se on children. The conclusions regarding alleged adverse health effects caused by diesel PM are based primarily on air pollution studies of PM_{10} where the exposure is a group-level or ecological measure. A number of studies have used exposure metrics related to traffic density as a semi-quantitative surrogate measure of diesel exposure (if based on truck traffic) or automobile exhaust.

A study done in 1996 at 3 California locations estimated that diesel PM comprised from 8-12% of total PM based on dispersion modeling and emission data from 1982 (Kleeman et al., 1999). The current proportion of diesel PM in ambient air is likely to be different than in the past, with some evidence that the levels and proportions are decreasing.

Specific Comments on Noncancer Air Pollution Studies

Thurston et al. (1997)

OEHHA said Thurston et al. (1997) reported that medication use for asthmatic children at summer camp "was a metric of severe air pollution effects associated with sulfate (a measure of particle pollution)."

Comment: *Thurston et al. (1997) found the most consistent associations were with ozone, that the associations with sulfate were highly influenced by one sulfate day when other pollutants were also high, and indicate the sulfate associations are not as important as OEHHA suggest.*

Thurston et al. Did not determine the contribution of diesel PM to the air pollutant mix in this rural setting. The authors considered ozone, rather than PM, the more important of the measured pollutants, in part because PM effects were primarily due too a single extreme value. Although diesel PM is a source of sulfate PM in ambient air, the amount of sulfates formed depends on the sulfur content of the fuel. Also, sulfates have not been identified as a surrogate to estimate the contribution of diesel PM to total PM (Winer and Busby, 1995). Without some marker to estimate diesel PM contribution it is not appropriate to attribute to diesel PM the health effects observed in this study.

The graphically displayed data suggest there is a threshold of perhaps 10 ug/m^3 sulfate below which there is not apparent trend for any of the health effects measured. The unknown concentration of diesel PM is likely to be below the apparent threshold of ~10 ug/m^3 sulfate observed in this study. The primary question unanswered by the OEHHA review is how these effects are associated with diesel PM, especially given that this is not a diesel study and diesel PM is likely below the threshold of effects.

Thurston et al. (1997) measured ambient concentrations of ozone, particulate acidity (H+) and sulfate (1.1-26.7 ug/m^3) from $PM_{2.5}$ (9am-9pm) and pollen. The health measures assessed were the daily number of asthma exacerbations (increased treatments), incidence of head and chest symptoms, and the change in am to PM peak flow (PEFR). The authors concluded the most consistent effects were associated with ozone, although they suggested fine PM might also play a role. Regression analysis showed ozone had the strongest associations with changes in PEFR and symptoms, while sulfate had the strongest associations with increased medication use. An increase of 100 ppb ozone (similar to the largest change during the high ozone summers) was associated with ~3% decline in PEFR/child, an increase of ~0.31 symptoms/day/child and an increase of ~0.20 daily asthma exacerbations/day/ child.

Ostro et al. (1995)

OEHHA said Ostro et al. (1995) concluded there were "significant associations between PM_{10} and asthma symptoms in 7-12 year old Los Angeles residents."

Comment: The only significant association with both PM_{10} and ozone was with shortness of breath. There were no significant associations with asthma signs and symptoms including wheeze, increased medication use and reductions in peak flow.

Symptoms, medication and peak flow from a panel of 83 children were recorded for 3 months and the associations with PM_{10}, ozone, NO_2, SO_2, pollen, molds and meteorological examined. Shortness of breath, but no other symptom (such as cough or wheeze), was associated with ozone and PM_{10}. There was no association with peak flow. The RR associated with 10 ug/m^3 increase in PM_{10} was 1.09 (1.009-1.16) (~9% increase in symptoms). The RR associated with a 10 ppb increase in ozone was 1.04 (1.016-1.07). The authors comment that the biological plausibility of these findings "would be strengthened by finding similar associations with wheezing." And they would be more consistent with Thurston et al. (1997) if similar associations had been observed with reductions in peak flow and increased medication use. There is no indication of the exposure to diesel PM and all measurements of pollutants are group-level measurements.

Delfino et al. (1997)

OEHHA said Delfino et al. (1997) found a "significant association between PM_{10} and bronchodilator use in asthmatic children."

Comment: This is an incorrect description of Delfino et al. (1997). Delfino et al. (1997) is a time-series study of respiratory emergency room (ER) visits that showed no associations with air pollution during one year of the study when concentrations were highest. The second year analyses showed associations of ozone, PM_{10}, $PM_{2.5}$ and SO_4 with elderly ER visits, but no associations with children < 2years old. There is no measure of DEP.

Delfino et al. (1997) is a time-series study of respiratory and nonrespiratory illness emergency room (ER) visits in Montreal for all ages for the summers of 1992 and 1993. Air pollutants measured included O_3, PM_{10}, $PM_{2.5}$, sulfate fraction of $PM_{2.5}$ (SO_4), and aerosol strong acidity (H+). There were no significant associations with ER visits during 1992 (33% of PM data were missing) so the analyzes focused exclusively on 1993. Concentrations of PM_{10}, $PM_{2.5}$, SO_4 and H+ in 1992 were 39%, 52%, 149%, and 283% higher in 1992 than 1993; 8-hour maximum and 1-hour maximum O_3 concentrations were 7% and 10% less in 1992 than 1993. The daily means for respiratory visits were higher for 1993 than 1992 for all age groups except children <2 years. Nonrespiratory visits were similar in both years. Respiratory visits in 1993 showed significant associations for ages 2-64. The more significant and strongest associations were for ages 65+ (PM and O_3), while only H+ was associated with respiratory visits for children < 2 years as seen in the RRs per mean value of each pollutant:

Relative risks (95% C.I.) for 1993 respiratory illness visits per mean air pollutant level by age group

Age Group	H+ (adj RH)	8-hr max O_3	PM_{10}	$PM_{2.5}$	SO_4
< 2-years	1.05(1.00-1.10)	NS	NS	NS	NS
65+	NS	1.22(1.09-1.35)	1.16(1.04-1.28)	1.12(1.02-1.21)	1.06(1.01-1.12)

These data are not consistent with the description of this study, are not consistent with the supposition that children are the most susceptible portion of the population, and are not consistent with the idea that the air pollutant of greatest concern is diesel PM.

- There were no measurements of diesel PM and no tenable way to estimate the E-R relationships with diesel PM. But under the OHHEA assumption that associations with PM are acceptable surrogates for diesel PM, the strongest associations were with O_3, not PM.
- This is not a study of asthmatic children and bronchodilator use. The study included all age groups and the illness was the broad general category of respiratory which included other illness besides asthma.
- The most susceptible sub-populations in this study were those over 64 years of age, with infants < 2-yrs showing a weak association with H+ only. Children 2-18 years of age showed no associations. These are results are not consistent with the idea of children being the most susceptible population.

Delfino et al. (1998)

OEHHA said that Delfino et al. (1998) "found significant association between asthma symptoms in children 9-17 years of age with both 1-hour and 8-hour PM_{10} measurements."

Comment: There were no measurements of DEP, which is likely to be low in the semi-rural community where this study was conducted. The measure of asthma symptoms (symptom diary index) was not associated with PM_{10} or ozone among asthmatics on medication.

Delfino et al. (1998) is a panel study of 25 asthmatics followed from August-October 1995. Symptom index was determined from diaries. The one subject with no severe symptoms was not included in the analysis. This community was selected because of relatively high O_3 levels and low PM_{10}. Those not on anti-inflammatory medication showed associations with PM_{10} and ozone, while those on medication did not show significant associations with either PM_{10} or O_3. These results differ somewhat from other studies in that the stronger associations were with PM_{10} rather than with O_3. Local sources of diesel PM were likely to be relatively low in this semirural community. Thus it is unclear how this study can be used to evaluate the role of diesel PM on asthma symptoms.

Burnett et al. (1994)

Burnett et al. (1994) was reported to have found the "largest percent increase in hospital admissions associated with PM_{10}.in the 0-1 year old age group of children in Ontario."

Comment: The purported differences in susceptibility between age group are not convincing or meaningful. The most statistically significant associations of 50 ppb ozone + 5 ug/m^3 sulfate were with the 35-64 year age group with a difference between the two age groups of only 3.2% (or 0.18 admissions/day) between the admissions attributed to ozone + sulfate. There were no estimates of DEP so it is not clear how this can be a study of the effects of DEP.

OEHHA suggested that children are affected more by air pollution than other age groups. The most sensitive to the effects of air pollution and the elderly the least effected. Burnett et al. (1994) estimated the highest percentage of hospital admissions were among the 0-1 year age group (13%, $p<0.05$), but the most significant association was among the 35-64 year age group (9.8%, $p <0.001$). The data indicate that in all the 168 acute care hospitals in Ontario the number of admissions each day attributed to 50 ppb ozone + 5.3 ug/m^3 sulfate were 0.68 admissions/day for 0-1 year infants, 1.25/day for ages 2-34, 0.86/day for ages 35-64 and 0.36/day for ages 65+. There is a 3.2% difference (or 0.18 admissions/day) between the "susceptible" 0-1 year infants and the most robust (presumably) part of the total population (ages 35-64). These differences seem too small to support the hypothesis of differences in susceptibility.

Burnett et al. (1994) measured only O_3 and sulfate, not PM_{10} or $PM_{2.5}$ or NO_x. Statistically significant associations were observed for both, although the strongest associations were with ozone. Burnett et al. (1994) note that others had found stronger associations of respiratory hospital admissions with O_3 than sulfate (Thurston et al.; 1992; Thurston et al., 1993) or PM_{10} (Cody et al., 1992). None of these studies have measured or estimated the exposure to diesel PM.

Infant Mortality: Woodruff et al. (1997), Bobak and Leon (1999)

Woodruff et al. (1997) in the U.S. and Bobak and Leon (1999) in the Czech Republic were said to have linked infant mortality with long-term exposure to PM.

Comment: Woodruff et al. Show implausible associations as the most susceptible low birthweight infants do not show an association with PM_{10} while the less susceptible normal birthweight infants show a significantly elevated association. These authors conclude there may be confounding from risk factors such as environmental tobacco smoke (ETS). Socioeconomic status should be added to the list of potential confounders. OEHHA incorrectly describe the study by Bobak and Leon as there was no association of infant mortality and measurement of PM (which was total suspended particulate).

OEHHA do not point out that the results of Woodruff et al. (1997) lack some internal consistency in that the presumably most susceptible LBW infants show a nonsignificant association while the less susceptible NBW infants show a significant risk for respiratory death.

Woodruff et al. (1997) evaluated the association of postneonatal mortality (infant death between 1 month and 1 year age) and the mean PM_{10} levels during the first 2-months of life. In this hybrid-ecological study, individual-level data of infant death and maternal/infant characteristics were linked with PM_{10} concentrations at metropolitan statistical areas (MSA). Mortality rates

were examined by low (12-28 ug/m^3), medium (28-40 ug/m^3) and high (40-69 ug/m^3) PM_{10} concentrations in the MSA. Adjustments were made for maternal race, maternal education, marital status, month of birth, maternal smoking during pregnancy, and average ambient temperature. The adjusted RRs per 10 ug/m^3 change in PM_{10} were 1.04 (1.02-1.07) for all causes, 1.12 (1.07-1.17) for SIDS for normal birthweight infants (NBW), 1.20 (1.06-1.36) for respiratory deaths for NBW, and 1.05 (0.91-1.22) for respiratory deaths of low birthweight infants (LBW).

Woodruff et al. (1997) note that their results are consistent with two similarly designed cohort studies: Six Cities and ACS (Dockery et al., 1993; Pope et al., 1995). ACS is more similar than Six Cities because the ACS cohort is national rather than regional like Six Cities. Woodruff et al. Conclude there may be confounding from additional risk factors for which they had no information (e.g., environmental tobacco smoke). They reason that the lack of control on additional risk factors was not important because in the Six Cities and ACS cohorts of adult mortality additional risk factors had not significantly altered the relationships between PM2.5 and adult mortality.

The reasoning that confounding is not important because it was not important in Six Cities and ACS is not adequate justification for concluding such risk factors are not confounding the association in this study. In the HEI reanalysis of the ACS cohort, adjustments for potentially confounding factors reduced RRs to nonsignificance. All cause mortality was reduced to 1.05 (0.85-1.30) after regional adjustment and including Relative humidity and SO_2 in the model. Cardiopulmonary mortality was reduced to 1.13 (0.91-1.40) after regional adjustment and including income, poverty, income disparity, unemployment, and education in the model. Education clearly modified the air pollution-mortality associations with individuals who had not completed high school having the highest risk of mortality while individuals who had completed high school "did not appear to have had increased risk." Krewski et al. (2000) thought education was a marker for a more complex set of socioeconomic variables that impact upon the level of risk. It is not clear whether Woodruff et al. Used a trichotomous education variable similar to Krewski et al. (2000) in their adjustment. And maternal education may not be adequate adjustment for SES as paternal education may be a more important adjustment for socioeconomic variables. Woodruff et al. Apparently did not adjust for regional effects, which Krewski et al. Found to be an important confounder. It is also important to note that there were no associations between air pollution and death from respiratory disease in either the ACS or Six Cities study. So it appears that in fact the results from Six Cities and ACS studies are not consistent with Woodruff et al. (1997). Further the reanalysis suggests that Woodruff et al. Did not control for important covariates that could change (reduce to nonsignificance) their risk estimates.

Bobak and Leon (1999) conducted an ecological study using aggregated response data on low birthweight and stillbirths, which were linked to district air concentrations for total suspended particulate (TSP), SO_2, and NO_x. The overall annual geometric mean for TSP was 68.5 ug/m^3 ranging from 33.5 to 115.5 ug/m^3. The study covered the years when the Czech Republic had some of the highest levels of air pollution in Europe. About 80% of TSP was PM_{10}.

Bobak and Leon (1999) found no significant adjusted associations of TSP or NO_x with low birthweight infants with ORs of 1.03 (0.95-1.11) and 0.99 (0.89-1.10) respectively; the OR for SO_2 was a significant 1.10 (1.01-1.20). The socioeconomic variables explained 50% of the variability in the data, while the pollutants explained only 2% of the variability. There were no significant associations of infant mortality and pollution, with adjusted ORs of 0.92 (0.74-1.15) for TSP, 0.90 (0.70-1.16) for SO_2 and 1.21 (0.89-1.64) for NO_x. However the R^2 was only 0.05 without pollutants and 0.04 with pollutants, indicating pollutants contributed essentially no information toward explaining variability in the data.

This study appears to have been misinterpreted by OHHEA, as there is no association of infant mortality associated with PM exposure.

APPENDIX 4:

TRAFFIC DENSITY AND RESPIRATORY EFFECTS

OEHHA Position: Since diesel exhaust is a "significant contributor to ambient PM levels in many urban environments," it is "plausible that many of the specific risk factors for children [that are related to] exposure to ambient PM apply with particular emphasis to diesel exhaust." The link of diesel exhaust to ambient PM is brought a little closer by citing studies where exposure is traffic density or nearness to vehicular traffic.

Comment: Socioeconomic status (SES) is a potentially major confounding factor that has generally not been considered in these studies. It is important because of the likely gradient of increasing SES with increasing distance from busy roads and the association of asthma with lower SES. There have been inconsistent adjustments for the home environment. Imputing traffic exposure from place of residence is problematic because much time is spent away from home. Home exposures are more important sources of NO_x and PM than traffic sources. And the prevalence of wheezing varies by a factor too great to be readily explained by the subtle differences in concentration related to traffic (Strachan, 1996).

There are potential confounders that are associated with both decreasing respiratory health and closeness to vehicle exhaust. As reported by Krewski et al. (2000), lower socioeconomic status appears to be an important risk factor for chronic mortality in the Six Cities and ACS cohort studies of PM air pollution. It is likely to be an important confounder in the assessment of diesel PM and distance from roadways. SES becomes a confounder because lower SES status is often associated with living closer to roadways, increased indoor exposure and worse respiratory health (including asthma symptoms). For example, environmental tobacco smoke (ETS), particularly maternal smoking, is associated with lower SES. ETS has also been linked with development of asthma, increased medications and earlier onset of asthma (Weitzman et al., 1990), increased prevalence of cough, phlegm, shortness of breath, wheeze, asthma and reduced lung function (FEV, FVC) (Cook and Strachan, 1997; Burchfiel et al., 1986), current asthma and current asthma in children and adolescents (Agabiti et al., 1999).

Strachan (1996) comments on some of the problems associated with interpreting studies of asthma and pollution from motor vehicles using proximity to major roads and/or traffic density as the exposure metric. The pollutants of major concern have been PM and NO_x. Both pollutants decrease with distance from the source, but the decline beyond 20 meters is small. Imputing traffic exposure from place of residence is problematic as home represents only a small part of daily exposure to ambient air and indoor sources (e.g. cooking fuels, environmental tobacco smoke) are more important sources of exposure to NO_x and PM. Strachan suggests that when there are significant associations between wheezing and traffic density the prevalence varies by a factor too great to be readily explained by the subtle differences in concentrations related to traffic density.

Strachan (1996) argues "for a cautious interpretation and careful consideration of possible confounding factors and reporting artifacts." His conclusion neither refutes nor confirms the

OHEEA conclusion regarding diesel PM and asthma, but offers a balanced scientific view of the complexity of the issue and some reassurance to people residing near busy streets--- The "failure of a statistically powerful study [Livingstone et al.).to show an association between local traffic density and prevalence of disease does not refute the possibility of a more general link between air pollution and asthma because place of residence is such a poor indicator of personal exposure to traffic related pollutants. Nevertheless, these findings do offer reassurance to city dwellers living close to busy roads that the location of their home does not place them or their children at substantially increased risk of asthma."

Specific Comments on Selected Studies

Wjst et al. (1993) and van Vliet et al. (1997)

Decreases in lung function (Wjst et al., 1993), and various chronic respiratory symptoms (van Vliet et al., 1997) were said by OEHHA to be associated with increased traffic density.

Comment: Wjst et al. (1993) estimated density of car traffic from census data and for the entire school district. NO_2 concentrations did not correlate with traffic, correlation with PM was not reported, and there was no estimate of diesel traffic. There were no significant associations with reductions in most measures of lung function (FEV1, FVC, and peak flow), and no association with increased airway reactivity. Risk ratios (RRs) were significantly increased (lower confidence interval > 1.0) for recurrent wheezing but not for other symptoms such as asthma, allergic rhinitis, recurrent shortness of breath, recurrent bronchitis, coughing.

Wjst et al. Conducted a cross-sectional study of fourth grade children in Munich. Data included lung function and respiratory symptoms on over 6,000 children who had lived in the same place for 5 or more years. Density of car traffic in the school district was estimated from census data on main streets. Each school district was allocated the street with the highest volume of traffic. Covariates included in the regression model for baseline lung function included parental history of asthma, height, weight, month of examination, number of cigarettes smoked at home, indoor use of gas or coal, and school education of parents for SES. The same covariates plus the number of people in the household were included in the logistic regression for symptoms.

Nitrogen dioxide concentration did not correlate (r=0.01) with traffic concentration and correlation with PM was not reported. And no mention was made of gas Vs diesel engines. So it is not clear how this study relates to exposure to diesel PM.

Exposure was a group-level variable so all the children in the same school district were assigned the same exposure. The mean percent changes in lung function associated with 25,000 cars/day were quite small even for a group. They included a 0.71% (-1.08 to +0.33) reduction in peak flow and reductions of <1% in flow at 25% and 50% of FVC (but not at 75%). However, there were no significant reductions in FVC or FEV and no increased airway reactivity as measured by cold air challenge. FEV is the most reproducible measure of both large and small airway obstruction and is an indicator of morbidity and mortality and asthmatics have what has been described as twitchy airways. So the observed effects do not suggest significant changes in the two most important measures of obstruction and restriction, or in airway reactivity. The

reduction in peak flow is not statistically significant since the upper confidence interval was positive showing a possible increase of 0.33%. The statement by OHEEA might be modified to indicate that apparently FEV and FVC reductions were not associated with increased traffic density. Odds ratios for symptoms significantly associated with motor traffic included 1.09 (1.00-1.08) for croup, 1.08 (1.01-1.16) for recurrent wheezing, and 1.10 (1.00-1.20) for recurrent shortness of breath. There were no significant associations for asthma, allergic rhinitis, upper respiratory infections, recurrent bronchitis or coughing.

Edwards et al. (1994)

Edwards et al. (1994) was reported to have found that asthma hospital admissions of preschool children in Birmingham, UK were related to traffic density.

Comment: Children < 5 years old admitted for asthma were more likely ($p<0.02$) to live in an area with high traffic flow than were children admitted for nonrespiratory reasons. However, Edwards et al. (1994) lacked information on potential confounders except age.

Edwards et al. (1994) is a case control study of cases admitted to the hospital for asthma compared to controls admitted to the hospital for nonrespiratory reasons. A community control group of children registered with general practitioners was also used, but the hospital controls are more appropriate since they are more likely from the same population at risk as the cases. Preschool children admitted for asthma were more likely to live in an area with high traffic flow than were hospital controls ($p< 0.02$). For those living < 500 meters from a main road there was a significant linear trend for risk of asthma to increase as traffic flow increased. Beyond 500 meters there was no trend. Hospital controls were more likely than community controls to be admitted if they lived within 200 meters of a main road irrespective of traffic flow ($p<0.02$), but there were no differences between cases and hospital controls.

The last comparison seems to indicate that compared to hospital controls there was no increased risk of asthma for those living within 200 meters of a main road irrespective of traffic flow. This result seems contrary to the linear trend of increased risk with traffic flow for those living < 200 meters from a main road. A weakness of this study is the lack of control for potential confounding risk factors as was done in Wjst et al. (1993). Without adjustments for risk factors that could be related to proximity to traffic, the conclusion that traffic density is a cause of increased asthma admissions is not confirmed and must await a study with better control of potential confounders. Van Vliet et al. (1997) comment that possible interpretations of the findings from Edwards et al. (1994) are limited because no air pollution data were collected and no information on potential confounders was available.

Van Vliet et al. (1997), Oosterlee et al. (1996), Brunekreef et al. (1997)

Various chronic respiratory symptoms were reported by OEHHA to be associated with increased traffic density among Dutch schoolchildren (van Vliet et al., 1997; Oosterlee et al., 1996). Also reduced lung function in the same population as van Vliet et al. Was associated with truck traffic density and black smoke (Brunekreef et al. (1997).

Comment: Exposure was the distance of each child's home from freeway where car and truck traffic density was based on counts. NO_x and black smoke (BS) concentrations decreased with increasing distance from the freeway, but there were no gradients for PM_{10} and $PM_{2.5}$ concentrations. BS correlated best with truck traffic, NO_2 with total traffic, while PM concentrations were variable and appeared to be poorly correlated to diesel traffic. Van Vliet et al. Found increased prevalence of chronic cough and wheeze among girls <100 meters from freeway, but no associations with rhinitis, asthma attacks or bronchitis. There were no significant associations for boys. Associations were mainly among children of low and intermediate SES. Brunekreef et al. (1997) reported reduced FEV and FVC among girls but not boys. Oosterlee et al. (1996) also reported associations of respiratory symptoms with NO_2 concentrations modeled on traffic among girls, but not among boys or adults.

Van Vliet et al. (1997) is a 1995 cross-sectional survey of 71% of 1498 school children 7-12 years of age who completed usable questionnaires on chronic respiratory symptoms. Exposure variables were distance of home from the freeway and truck and car traffic density based on counts in 1993. The 13 schools were all less than 1000 meters from a major freeway in South Holland. Ambient measurements of PM_{10}, $PM_{2.5}$, black smoke (BS) and NO_2 were made in 2 of the 6 area at 4 distances from the freeway. There were no concentration gradients for either PM_{10} or $PM_{2.5}$ but slight gradients for BS and NO2 in the two sights where they were measured. Concentrations of NO_2 and BS showed a 4-fold difference between classrooms, differences that were much greater than the concentration gradients from the freeways.

The only statistically significant findings overall regarding respiratory symptoms were decreased RRs for atopy associated with BS and NO_2 concentrations in school. Girls living within 100 meters of freeway compared to those > 100 meters showed significant 2.5-fold and 3-fold increased risks of chronic cough and wheeze respectively, nonsignificant 2.3-fold increased risk of rhinitis, and no increased risks of asthma attacks or bronchitis. Symptoms were increased 2-fold or more when the exposure metrics were density of truck traffic and BS concentration in school, but none were statistically significant. For boys there were no associations for any of these exposures or symptoms as RRs were generally close to 1.0. Stratified analyses suggested that the associations were "mainly restricted to the children of intermediate and low SES," although the associations with traffic-related indicators remained after adjustments for a variety of environmental exposures at home.

This study has improved measures of potential confounding risk factors at home, limited air pollution measurements, and traffic counts for both cars and trucks to estimate traffic density. The results are suggestive that PM_{10} and $PM_{2.5}$ may not be good surrogate measures of diesel PM exposure. BS showed a gradient and correlated better with truck traffic density than with automobile or total traffic, unlike NO_2 which correlated best with total traffic. The finding of associations with cough and wheeze among girls but not among boys is consistent with Oosterlee et al. (1996) who also found an association of wheeze and traffic density among girls, but not among boys. They also reported no association among adults. Most studies have not stratified by gender, and it is not clear why an association would be found for girl but not boys. A major finding in this study and the lung function study by Brunekreef et al. (1997) is the inconsistent findings for boy and girls.

In this same population of school children Brunekreef et al. (1997) evaluated lung function and reported similar results for lung function with regard to associations with girls but not boys. OHHEA correctly notes that decrements in lung function were more strongly associated with BS than with general traffic statistics and with truck traffic density than with automobile traffic density. Also there was a clear exposure-response relationship between truck traffic density and reduced FEV1 for children living less than 300 meters from a roadway.

Reduced FVC and FEV_1 were associated with density of truck traffic and BS concentrations in school for girls living < 300 meters of freeway. The reductions were 6-8% per 10,000 trucks and 10 ug/m^3 BS for girls. These findings contrast with essentially no associations for boys-- 1-2% nonsignificant decreases associated with truck density and 2-4% increases associated with BS concentration. There was a clear exposure-response trend and the effect on lung function was said to be even greater for children living within 100 meters. Although there was adjustment for home environmental conditions and parental education, it was not stated whether lower SES was related to the reductions in lung function as they were for increased symptoms. The authors comment that the predominance of the associations in girls and not boys is intriguing. The reasons for this apparent inconsistency are not clear. Unlike the potential gender difference in reporting symptoms there should not be a similar bias in the more objective measures of lung function. It is not clear whether lower SES is also related to reduced lung function. And it is not clear why FVC should be related to traffic density. Airflow obstruction caused by some level of PM is plausible, but fibrotic changes are implausible and the degree of airflow obstruction is unlikely to be the cause of reduced FVC. And it is unlikely that reduced effort would be associated with distance of residence from increased traffic density, or that girls would be preferentially effected by acute exposures.

Oosterlee et al. (1996) is a cross-sectional respiratory survey of 106 children (0-15 year) and 673 adults on busy streets compared to 185 children and 812 adults living along quiet streets in the same neighborhood. Exposed and control residents were selected on the basis of NO_2 concentration estimated from a mathematical model that used parameters such as traffic density, kind of fuel and vehicle, emission rates and typography. NO_2 concentrations ranged from 62 to 80 ppb, which corresponds to 10,000 to 30,000 vehicles/24 hours. ORs for children were estimated with adjustments for age, sex, mother's education, ETS, type of heating, pets and crowding; similar adjustments were made for adults. Adjusted ORs were generally slightly higher than crude ORs for the 16 respiratory symptoms, perhaps because of the higher prevalence of home dampness in the control population and/or 14% nonresponse mainly among the exposed children with symptoms and adults with health children in the control population.

There was a significant OR of 2.2(1.1-4.6) for ever using respiratory medication associated with NO_2 in children 0-15 years old. For boys there were no significant associations and for girls there significant ORs of 4.4 (1.4-13.6) for ever wheeze, 5.3 (1.1-25) for wheeze in past year, 4.8 (1.3-18) for ever attacks of dyspnea with wheeze, 15.8 (1.4-174) for attacks of dyspnea with wheeze in the past year, and 2.9 (1.1-7.9) for respiratory medication. The only significant OR for adults was 1.8 (1.1-3.0) for dyspnea occasionally during walking.

Oosterlee et al. (1996) only showed significant associations for girls, and not for boys or adults.

Studies to Add: (Venn et al., 2000), English et al. (1999), Livingstone et al. (1996)

Several Studies showing no associations between respiratory health and traffic should be added to the analysis by OHHEA.

Comment: Venn et al. (2000) found that traffic activity around primary and secondary schools was not a major determinant of wheeze or asthma symptoms in children. Ecological analysis showed substantial variation in wheeze between schools that did not seem to be due to road traffic in the individual-level analysis. Road traffic was directly measured and adjustments for factors in the home environment (e.g. social class, parental smoking) were attempted.

English et al. (1999) used geographic information systems (GIS) and pollutant dispersion models to estimate traffic flow. The number of medical care visits for asthma showed no statistically significant associations with traffic flow although heavy exposure may increase the risk of medical care visits for girls. The authors interpret their data as suggestive that heavy exposure to traffic might exacerbate symptoms in those with asthma, but found no relationship with the initiation of asthma.

Livingstone et al. (1996) found no increased risk of asthma associated with living close to busy roads for adults or children in a hospital case control study of hospital admissions for asthma. Cases had a slightly higher deprivation score suggesting somewhat lower SES. Adjustments were made for sex, practice and age. There was no increase in risk of asthma associated with living close to busy roads for adults or children with the dichotomous exposure metric of less than 150 meters from a busy road Vs greater than 150 meters. There was also no association when residence was a continuous variable. The OR was 1.0 (0.84-1.19) for those age 16-64 and 0.96 (0.78-1.22) for those age 2-15.

APPENDIX 5:

IMMUNOLOGICAL EFFECTS

Several studies are cited in support of the hypothesis that diesel PM enhances allergic responses to allergens, and that DEPs could induce immunological allergic reactions as well as localized inflammatory responses in humans.

Comment: These are experimental studies, either in vivo or in vitro. It is not appropriate to extrapolate the results to the general population. The in vivo studies instilled an excessive concentration of DEP in the nose. Extrapolation is inappropriate since the nose is not the major deposition and the dose is excessive and atypical of even excessive ambient concentrations. The in vitro studies extracted polyaromatics (PAHs) from DEP using an organic solvent rather than lung surfactant. Thus PAHs could have been extracted that are not normally bioavailable. Whether cells in culture respond as cells in vivo is not reported, and whether the doses to cells in culture is similar to cell in vivo is unknown.

The authors assert that exposure to PAHs may explain in part the increased otitis media rates noted in children exposed to tobacco smoke, and infer that exposure to DEP containing PAHs may produce a similar risk. However, no studies are cited to support this novel hypothesis.

The authors infer that DEP may produce immunosuppressive effects. However, no experimental studies with DEP are cited to support this hypothesis. Rather, general information from in vitro studies and studies in animals exposed to PAHs are cited. Since only indirect evidence is available to support the hypothesis, and the data demonstrating a differential susceptibility in children is so limited, is unclear why the conclusions are so definite regarding a "clear and disproportionate impact on infants and children."

Diaz-Sanchez et al. (1996, 1994)

Diaz-Sanchez et al. (1996, 1994) used intranasal instillation of 0.15 mg, 0.30 mg, and 1.0 mg of DEPs in a saline solution. The 1994 paper suggests 0.30 mg is approximately equivalent to breathing the outdoor air in Los Angeles for 24 hours. The 1996 paper suggests a 0.2 mg. dose is roughly equivalent to breathing Los Angeles air for 24 hours. The 0.2 mg was also equated to sitting behind a bus, which was said to expose a person to a similar amount but in one dose, thereby simulating the bolus effect of the instillation exposure.

The exposure is not similar to that normally experienced. First the dose is instilled in one bolus in a localized area of the nose. Free-ranging individuals are breathing a dilute mixture of submicron particles through the mouth or nose with perhaps 25% deposition (Terada et al., 1997). Nasal deposition is <5% or so. Instillation of 150 ug DEP with 100% deposition is equivalent in concentration to a dose of about 600ug inhalation at 25% deposition. Then instillation of 150 ug DEP in the nose is similar to breathing over 24 hours a concentration of 30-40 ug/m^3 DEP. OHHEA estimates the average concentration of DEP in the South Coast Air Basin is 3.6 ug/m^3. The equivalent concentration for a 1-hour bolus of 150 ug (as a simulation of

riding behind a bus) is a concentration of 720-960 ug/m^3. Boluses of 0.3 mg and 1 mg produce exposures that are 2 -7 times greater an even more dissimilar to ambient concentrations of even PM_{10}, much less DEP. In sum, the instillation of the DEP bolus is dissimilar to normal inhalation exposures both in magnitude and location.

Terada et al. (1997) and Takenaka et al. (1995)

Terada et al. (1997) and Takenaka et al. (1995) were two of the studies said to have induced immunological allergic reactions as well as localized inflammatory responses in humans.

Terada et al. (1997) examined the effects of DEP and polyaromatic hydrocarbons (PAHs) extracted from DEP using an organic solvent (dichloromethane). The observations were not in humans but in cell cultures of human eosinophils, mucosal microvascular endothelial cells and nasal epithelial cells. The authors concluded that their findings DEP may play an important role in promoting the nasal hypersensitivity induced by enhanced eosinophil infiltration of epithelium and eosinophil degranulation.

Several factors in these experiments should be recognized before extrapolating to the health effects on free-ranging individuals of exposure to DEP in ambient air. The cells are from the nose rather than the lung where most of the DEPs are deposited. The experiment is in cell culture rather than in vivo. The PAHs are extracted using dichloromethane rather than a lung surfactant, so bioavailability may be different in vivo compared to in vitro. Although the dose was said to be equivalent to the annual average of 24 ug/m^3 DEP in Tokyo, it is not clear that one can estimate a physiological dose for in vitro exposures.

Takenaka et al. (1995) showed that PAHs extracted from DEP using the solvent dichloromethane enhanced the production of IgE from human B cells. The authors conclude that this provides evidence that this provides evidence that this may be an important factor in the increase in airway allergic disease. However, note that the bioavailability of the PAHs from DEP was not evaluated and the PAHs were not extracted using lung surfactant but an organic solvent. And the enhancement was from cells in vitro, not in vivo. It is also not clear what concentration of PAHs is a physiological dose in vivo. These findings need to be observed in vivo at concentrations found in real life before we can assess their importance in the expression of airway allergic disease.

Response: As noted in the response to Comment 5, extrapolation of results from experimental studies to the general population is part of the foundation of scientific risk assessment. The studies cited in the diesel exhaust prioritization document (Diaz-Sanchez et al., 1994, 1996, 1997; Terada et al., 1997, Takenaka et al., 1995) indicate that the exacerbation of asthma by diesel exhaust is due specifically to a modulation of the immune system, and not because of a general irritant effect. It should also be noted that acute healthy adult human exposures to concentrations of diesel exhaust particulate matter (300 µg/m^3) approximately one order of magnitude greater than peak diesel exhaust concentrations noted near freeways demonstrated a marked leukocytic airway infiltration accompanied by enhanced chemokine and cytokine production (Salvi *et al.*, 2000) Since the prevalence of asthma is much higher among children

than among adults (CDC, 1996a,b), exacerbation of asthma by diesel exhaust will put more children at higher risk of adverse health effects than adults.

The studies cited above were designed to determine the mechanisms by which diesel exhaust particulate matter modulates immune system response. With regard to the studies performed by Diaz-Sanchez et al. (1994, 1996, 1997), there is no reason to believe that a bolus dose of diesel exhaust particulate matter would have mechanistically different immune system effects compared to the same dose spread out over a period of time. The studies by Terada et al. (1997) and Takenaka et al. (1995) are mechanistic studies which support the findings of Diaz-Sanchez et al., and are useful in determining how diesel exhaust exacerbates asthma. They are not being used in the present context as the basis of a quantitative risk assessment.